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ANNALS OF
INTERNAL MEDICINE

VOLUME 26 JANUARY, 1947 NUMBER 1

# SURGICAL TREATMENT OF BRONCHIECTASIS *

By EARLE B. KAY, M.D., *Cleveland, Ohio,* RICHARD H. MEADE, JR., M.D., *Chicago, Illinois,* and FELIX A. HUGHES, JR., M.D., *Memphis, Tennessee*

PERMANENT cure of bronchiectasis can be obtained only by pulmonary resection. The operative mortality and morbidity are today so small in contrast to that inherent in the disease that operation can be recommended without hesitation. The opinions in this report are based on the treatment of 390 patients with bronchiectasis at this Chest Center and at Percy Jones General Hospital during the past three years. During this period there have been 220 consecutive lobectomies with only one death, an incidence of 0.4 per cent. This fatality was the fourth patient to be operated upon at this hospital. One hundred and eighty-four lobectomies were performed for bronchiectasis, 20 for pulmonary cysts, 11 for chronic pulmonary suppuration, three for bronchial adenomas associated with suppuration, and two for basilar tuberculosis. The bronchiectasis in the patients not operated upon was either too minimal, too patchy and diffuse, or too extensive. A small number of patients refused operation. The bronchiectasis in five patients involved the entire lung and required pneumonectomy. The purpose of this paper is the presentation of the surgical management of patients having lobectomies, with particular reference to those having bronchiectasis. The selection of patients for operation, the preoperative, operative, and postoperative management, and complications are discussed. Pulmonary function before and after operation as determined by bronchospirometric studies in a smaller group of patients is presented.

The clinical course of patients with bronchiectasis is known to all. It is characterized by chronic sepsis, varying degrees of debility, and usually recurring attacks of pneumonia. There may be remissions with relative freedom from symptoms. This does not mean that the bronchiectasis is healed. The degree of disability is largely dependent on the degree of sepsis

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which in turn is dependent largely on the adequacy of bronchial drainage. The destructive changes in advanced bronchiectasis are permanent and irreversible.

In the development of this disease, the ciliated columnar epithelium is frequently ulcerated and replaced by non-ciliated cuboidal or squamous epithelium and the normal elastic tissue and smooth muscle fibers are partially or completely replaced by granulation or scar tissue. Because of the loss of the normal cleansing action of the bronchial tree due to the loss of the ciliary action of the mucous membrane and the peristaltic action of the bronchial wall, stasis of exudate and resulting infection occur.

The prognosis of patients with untreated or medically treated bronchiectasis is poor. Roles and Todd [1] reported a mortality rate of 47 per cent in the 49 non-surgical cases followed by them over a six-year period. Perry and King [2] followed 260 untreated or medically treated bronchiectatic patients over a 12-year period. The mortality rate for the traced males was 36 per cent, as compared to 26 per cent for females. The mortality rate as shown by them was higher when the bronchiectasis was cystic (55 per cent), or saccular (37 per cent), than when cylindrical (13 per cent). Patients having bilateral bronchiectasis had a 42 per cent mortality rate during this 12-year period in comparison to 25 per cent for unilateral cases. This illustrates the higher mortality rates in the more severe and extensive degrees of the disease.

Apart from the mortality, the morbidity is also considerable. Thirty-five per cent of the 100 patients followed by Riggins [3] during a 10-year period were unable to work because of the severity of their disease or psychological effects of the foul-smelling, productive cough. An additional 40 per cent worked only part time, their work being frequently interrupted by exacerbations. Many patients have suffered the effects of chronic sepsis for so long that not until after a lobectomy do they realize that it was possible to have felt better. Some patients with bronchiectasis live out their life span; one can not foretell those who will.

Conservative therapy to improve bronchial drainage, combat infection, and improve the general physical condition of the patient is of value and should be employed. Postural, as well as bronchoscopic drainage, breathing and coughing exercises, eradication of other foci of infection, high vitamin, high caloric diets, supplementary vitamin therapy, medicaments to thin viscid bronchial exudates, as well as chemotherapy, are valuable adjuncts in the management of bronchiectatic patients. Penicillin [4] is of value in the treatment of the recurrent pneumonic episode. It also decreases the amount of sepsis and intoxication during the interval stages. In no patient with advanced bronchiectasis, however, can the sputum be made to disappear completely. When penicillin is discontinued symptoms invariably recur in a short period of time. Penicillin in no way improves the underlying pathological changes and as such is no safeguard against exacerbation of infection and symptoms. One can temporize with the disease over a period of years

by symptomatic treatment. Even though apparent improvement results, no one denies the part played by chronic sepsis in the development of degenerative changes in the heart, liver, kidneys, and blood vessels. Death from bronchiectasis usually results from pneumonia, septicemia, pericarditis, right heart failure, hemorrhage, or empyema. The possibility of these hazards is present as long as the bronchiectasis exists. One must then decide between palliative therapy and a permanent cure.

*Selection of Patients for Operation:* Decision as to operative therapy depends upon the amount of disability, the extent of the destructive changes, and the physical evidence of chronic intoxication. It is obvious that patients with bronchographic evidence of bronchiectasis who otherwise show no significant clinical evidence of the disease do not require surgical treatment until such a time as otherwise indicated. Furthermore, patients with minimal bronchiectasis can be cared for conservatively, and those whose bronchiectasis involves all five lobes are beyond the realms of surgical treatment and must be cared for conservatively. If there are no other contraindications to operation, lobectomy is recommended.

Bronchiectasis is bilateral in approximately 30 per cent. Studies, such as the one by Perry and King, show a mortality rate as high as 42 per cent for patients with bilateral bronchiectasis during a 12-year period. The associated morbidity is even greater. In view of this, a definite attempt should be made to treat these patients. Those patients with advanced bronchiectasis on one side and minimal on the other who had lobectomies on the more extensive side were so improved by operation as to make this procedure well worth while.

Lobectomy, until recently, was largely reserved for those patients whose bronchiectasis was either primarily unilobar or unilateral. With the lowered morbidity now associated with lobectomy, the field of operability has increased to include those patients with extensive bronchiectasis on one side and minimal on the other, or with extensive bilateral bronchiectasis as long as the right upper lobe and upper aspect of the left upper lobe are free from disease, and whose cardiorespiratory reserve is adequate (figure 1). In the group having lobectomies for bronchiectasis, 36 patients had bilateral disease. In 28 one side was minimal enough not to require lobectomy, and in six bilateral lobectomies were performed. In the other two the second operation is contemplated in the near future. One patient had the right middle and lower lobes removed followed six months later by removal of the left lower lobe and lingula. The average interval between the two operations was four months.

*Preliminary Studies:* Adequate bronchograms outlining all five pulmonary lobes should be made with roentgenograms taken in the postero-anterior, right and left oblique, and lateral projections in order to ascertain with certainty the degree and distribution of the bronchiectasis present. If necessary, bronchographic examination should be repeated until this information is obtained. Careful bronchoscopic examination should be carried

out to determine from which lobes most of the exudate is escaping, the presence of an unduly acute inflammation of the bronchial mucosa, to eliminate the possibility of the bronchiectasis being secondary to bronchial occlusion due to foreign bodies or tumors and to improve bronchial drainage.

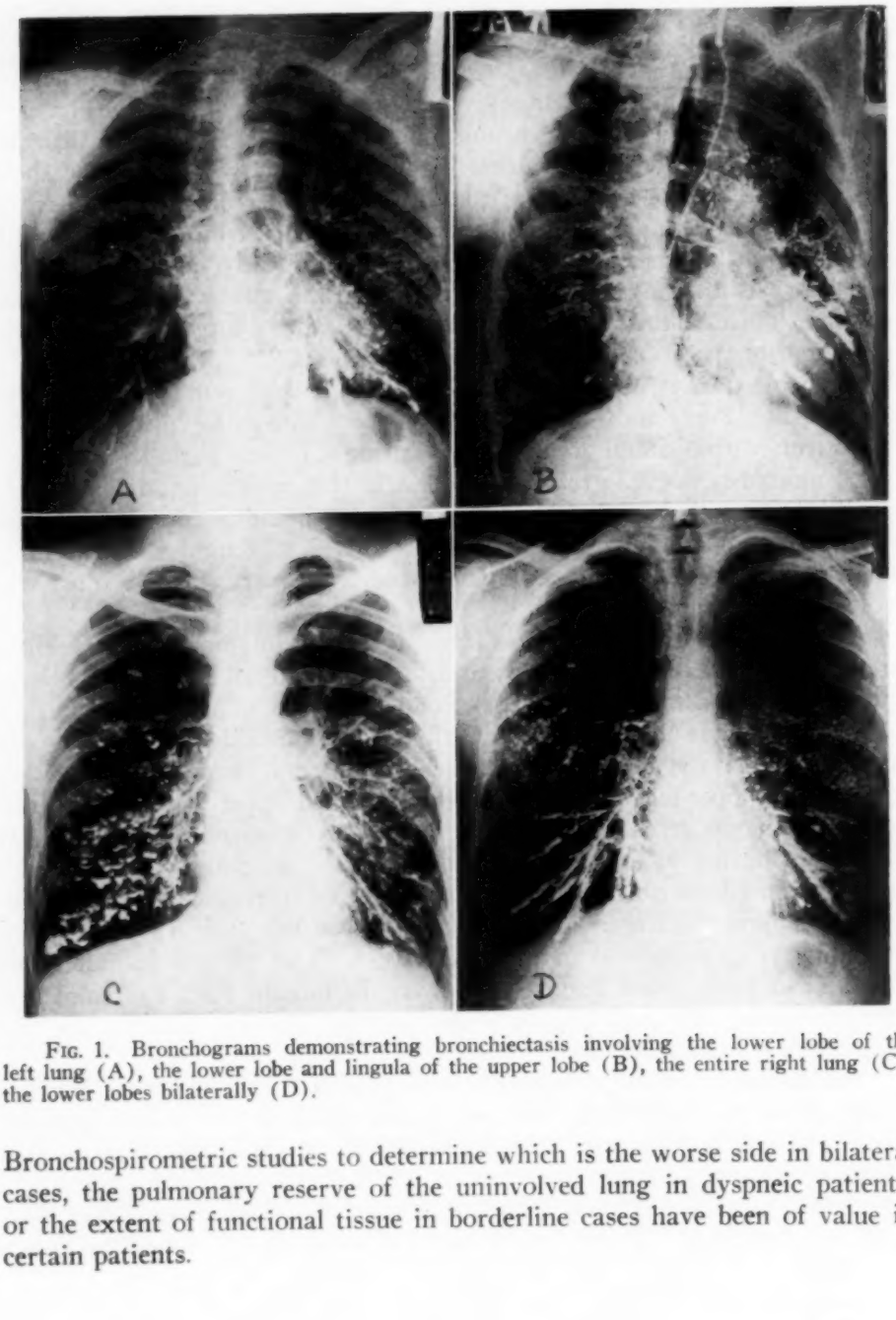


FIG. 1. Bronchograms demonstrating bronchiectasis involving the lower lobe of the left lung (A), the lower lobe and lingula of the upper lobe (B), the entire right lung (C), the lower lobes bilaterally (D).

Bronchospirometric studies to determine which is the worse side in bilateral cases, the pulmonary reserve of the uninvolved lung in dyspneic patients, or the extent of functional tissue in borderline cases have been of value in certain patients.

*Preoperative Management:* The operation should be postponed until the patient is in as good a preoperative condition as possible. A period of at least four to six weeks should elapse following the bronchographic examination to allow elimination of the iodized oil for this may cause postoperative pneumonitis. During this period of time the patient is placed on a high vitamin, high caloric diet with supplementary vitamin therapy if necessary.

The vitamin C and plasma protein components of the blood should be normal. Careful otolaryngological examination should be made and any infection so found controlled. Postural drainage should be employed three to four times daily if found effective. A one to two week course of intratracheal penicillin has been found to be of value in patients with copious amounts of sputum and with severe bronchitis. Those who have associated sinusitis are benefited by nebulized penicillin. Patients severely ill over a long period of time should have a careful medical evaluation of possible cardiac, hepatic, and renal complications and the appropriate treatment given. After the patient is so prepared, operation is performed. Intramuscular penicillin is given the evening before operation.

*Operative Technic:* No detailed discussion of the operative technic will be given. All of the operations except the first two have been done by individual ligation technic. The rôle of the anesthetist in intrathoracic operations is an important one, and his management of the anesthesia and patient determines largely the ease and safety with which the operation can be performed. The maintenance of a clear airway by efficient intratracheal and intrabronchial aspiration through an intratracheal tube of large enough caliber to allow easy aspiration and firm enough to resist collapsing is essential. The posterolateral approach with resection of the seventh rib, or the lateral approach with resection of the sixth rib has been found to give good exposure. The antero-lateral approach with resection of the fifth rib and with the head of the operating table elevated 15 to 20 degrees is of value in patients with bilateral bronchiectasis or in patients having copious amounts of sputum. This in combination with early operative occlusion of the bronchus keeps the exudate in the bronchiectatic abscesses rather than allowing it to drain out into the main bronchi to cause obstruction and perhaps aspiration into the opposite lung. Secure closure of the bronchial stump determines largely the postoperative course. The bronchus should be amputated high to prevent puddling of secretions at this site afterwards. The end of the stump is closed by over-end interrupted black silk sutures. Occasionally, two to three mattress sutures have been placed slightly proximal to this row. They are inserted longitudinally to prevent interference with the blood supply to the bronchial stump. The ends of these sutures are left long and are later used to seal down a small pleural flap developed from the mediastinal pleura directly beneath the bronchial stump. This flap is used to reinforce the bronchial closure. Silk technic is used throughout. All pleuritic adhesions between the upper lobe and chest wall are severed, for it is felt that these otherwise prevent the upper lobe from read-

justing itself to the larger space allotted to it. Closed intercostal drainage is maintained usually for 48 hours. It is essential that the thoracotomy tube is functioning properly during this period of time to allow effective drainage of the residual air and serum to insure immediate reëxpansion of the remaining lobe. All patients have bronchoscopic aspiration of the intrabronchial secretions immediately postoperatively to avoid postoperative bronchial occlusion, atelectasis, and delayed reëxpansion. Blood transfusions are begun at the onset of the operation and continued throughout its course; usually 1,000 to 1,500 cubic centimeters of blood suffice.

*Postoperative Management:* Adequate oxygenation is provided by means of an oxygen tent or intranasal oxygen. It has usually been possible to discontinue this after 12 to 24 hours. The maintenance of an open tracheobronchial airway is essential to early reëxpansion of the remaining lobe and obliteration of the pleural space. This is accomplished by frequent intratracheal aspiration, insistence upon coughing, deep breathing exercises, and frequent change in position of the patient. Intramuscular penicillin is given for seven days in the dosage of 25,000 units every three hours. The patient routinely is gotten up by the third postoperative day. He may get up sooner in order to void, if necessary. A temporary phrenic nerve paralysis is performed during the postoperative period if the patient complains of tightness in the chest, in cases where an emphysematous lobe has been removed and over-distention of the remaining lobe is not desired, or in patients having high lingulectomies or middle lobe lobectomies in combination with the lower lobe lobectomies.

*Complications and Results:* In only one patient was significant shock from blood loss encountered. Lesser degrees of shock in other patients were only transitory and responded readily to treatment. During the postoperative period bronchopleural fistulae with resulting empyemata developed in 20 instances, an incidence of 9.7 per cent. Most of these developed during the initial phase of this series. This incidence has been reduced to 5 per cent for the last 100 lobectomies performed. Postoperative atelectasis occurred in only five instances. One of these was in the patient who had the right middle and lower lobe lobectomy followed six months later by a left lower lobe lobectomy and lingulectomy. On the third postoperative day atelectasis of the remaining portion of the left upper lobe developed that persisted in lesser degrees for the next three days. During this period of time the patient was maintained on only the right upper lobe. The intermittent use of intranasal oxygen sufficed. The lobe was completely reaerated within three days' time with the repeated use of intratracheal aspiration. It is our opinion that postoperative pulmonary collapse is due primarily to intrabronchial exudate and occlusion. If the bronchi are kept free from secretions by frequent coughing and aspiration, this complication can be prevented. Two patients developed hemothoraces thought due to injury of the intercostal vessels at the time of insertion of the thoracotomy tubes. Six patients developed postoperative jaundice. It was difficult to

determine with certainty whether the jaundice was secondary to blood transfusions or a concomitant hepatitis, in that a number of cases of hepatitis occurred in the hospital at that time.

There was no complication from the contralateral lung in patients with bilateral bronchiectasis; however, the postoperative care and treatment in these patients was most rigid. One patient developed a postoperative cerebrovascular accident, thought probably due to a septic embolus. He was treated with both penicillin and streptomycin. A trephine was performed six weeks postoperatively and a small sterile, cystic cavity was found. This was evacuated and the patient is now well. Penicillin is given in the blood during operation to minimize the likelihood of this complication.

There was only one operative death in this series of 220 consecutive lobectomies. This was the fourth case to be operated upon at this hospital.

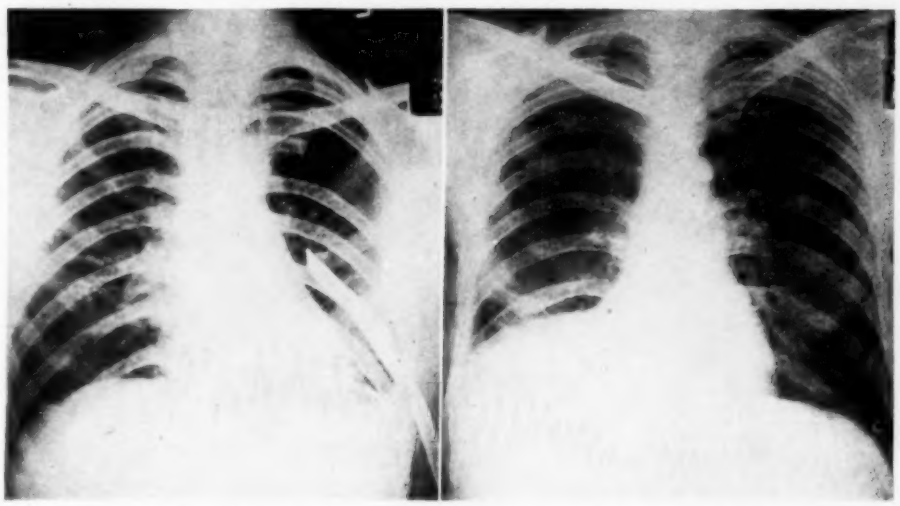

FIG. 2. (left) Roentgenogram taken 24 hours postoperatively demonstrating complete reexpansion of the remaining upper lobe. Thoracotomy tube is removed after 48 hours.
FIG. 3. (right) Postoperative roentgenogram of patient whose bronchospirometric examination is demonstrated in chart 3.

The patient died 24 hours after operation from pulmonary and cerebral edema. The operation was long and technically very difficult. A clear tracheobronchial airway and proper oxygenation were difficult to maintain during operation.

Early reëxpansion (within 24 hours) (figure 2) of the remaining pulmonary tissue concomitant with adequate drainage of the pleural space not only reduces postoperative convalescence and morbidity, but lessens postoperative pleural pain and allows better pulmonary function on the operated side as shown by bronchospirometric studies than would have been possible if any degree of pleural thickening developed.

Bronchospirometric studies performed on 26 patients postoperatively demonstrated that the pulmonary function of the remaining pulmonary tissue

on the operated side is dependent largely on the postoperative pleural complications. The objective of operative technic today is not just the removal of the pulmonary lobe, but its removal in such a manner as to be followed by an uneventful convalescence. Chart 1 demonstrates the bronchospirometric findings of a patient one month following a left lower lobe lobectomy. It illustrates the normal oxygen consumption and ventilation on the operated side in a patient whose postoperative convalescence was entirely uneventful. The operated side contributed 53 per cent of the total oxygen consumption and 52 per cent of the total ventilation. This is higher than would be expected unless some disease was present in the opposite side. Similar studies performed on a patient one year following lobectomy and another three

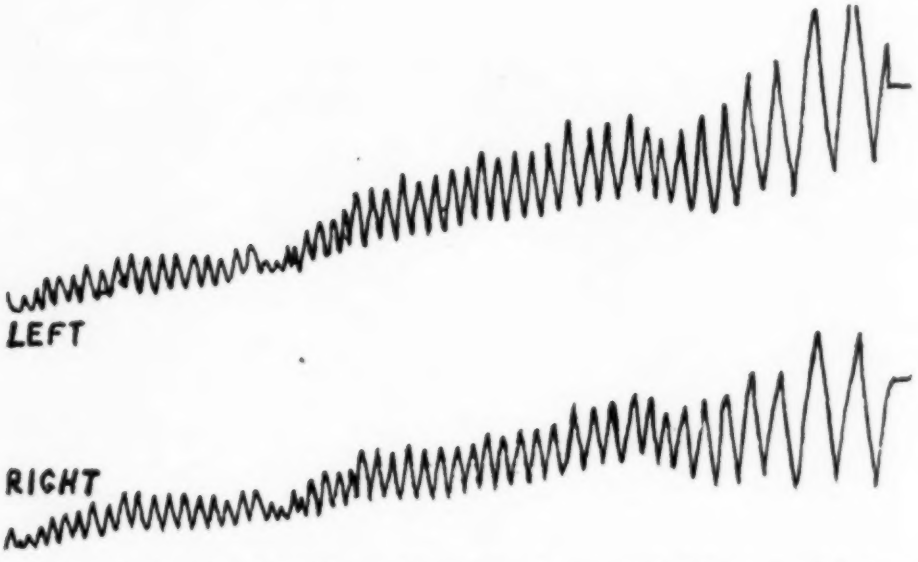


CHART I. Bronchospirometric tracing performed one month following a left lower lobe lobectomy. The operated side (left) contributed 53 per cent of the total oxygen consumption and 52 per cent of the total ventilation.

years following lobectomy showed that the pulmonary function on the operated side was almost within normal limits. Evidence of the decreased pulmonary function subsequent to pleural thickening is illustrated by chart 2. This patient with advanced bronchiectasis of the left lower lobe developed pneumonia and empyema on the right side in December 1943. Because of the persistence of a chronic productive cough following healing, bronchographic examination was performed which showed extensive bronchiectasis of the left lower lobe. A left lower lobe lobectomy was performed April 10, 1945. The patient withstood the operative procedure well, and the postoperative convalescence was entirely uneventful. Bronchospirometric examination performed seven weeks postoperatively demonstrated that the operated side contributed 76.4 per cent of the total oxygen consumption and

69 per cent of the total ventilation. If it had been appreciated by bronchospirometric examination preoperatively that the pulmonary function of the right lung was this poor, lobectomy would have been done with some trepidation. Chart 3 demonstrates the bronchospirometric tracing in a

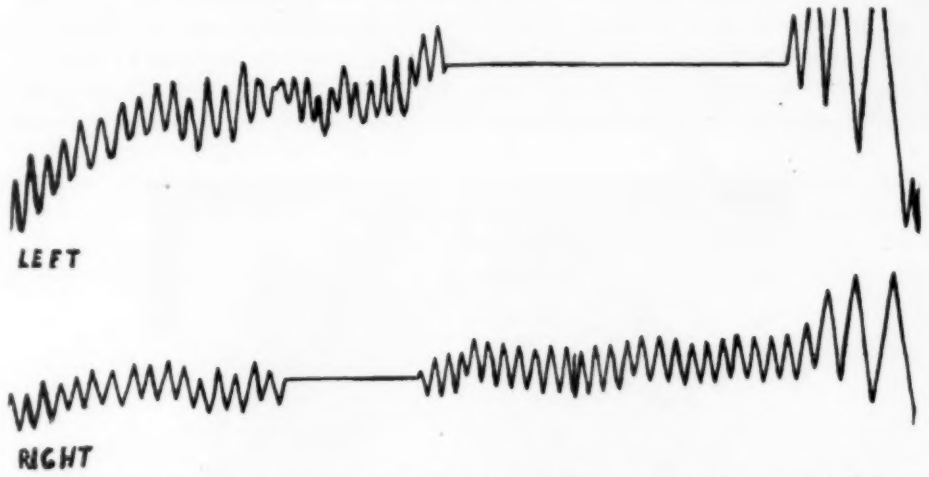


CHART II. Bronchospirometric tracing performed seven weeks following a left lower lobe lobectomy in a patient who had residual dysfunction of the right lung secondary to a pneumonia and empyema. The decreased pulmonary function secondary to the pleural thickening on this side was evident from this examination. The operated side (left) contributed 76.4 per cent of the total ventilation.

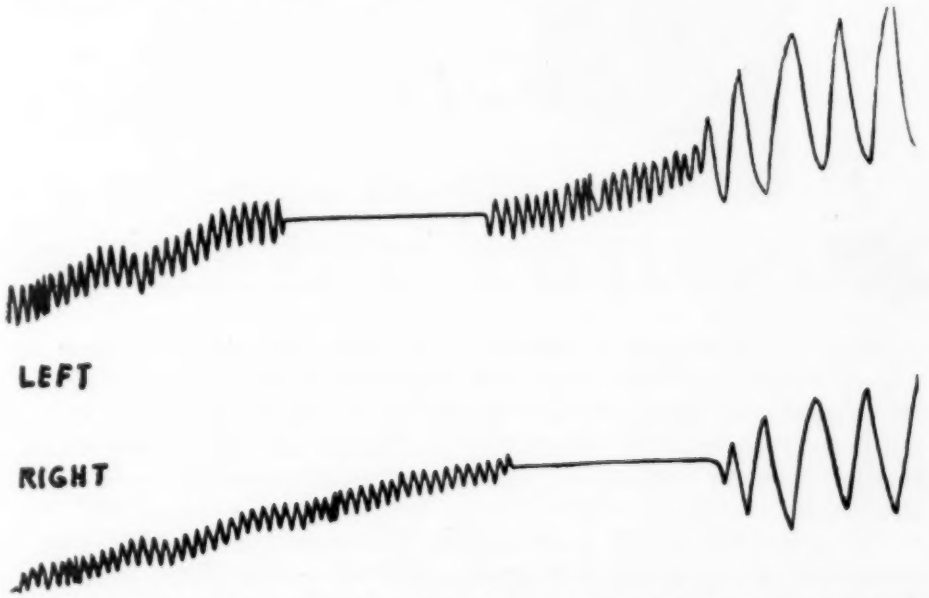


CHART III. Bronchospirometric tracing performed eight weeks following a right middle and lower lobe lobectomy. The phrenic nerve was crushed eight days postoperatively to prevent overdistention and emphysema of the upper lobe. The operated side (right) contributed 47 per cent of the total oxygen consumption and 43 per cent of the total ventilation.

patient having a right middle and lower lobe lobectomy in which the phrenic nerve was crushed during the postoperative period in order to prevent over-distention of the upper lobe (figure 3). It is noted that the function of the operated side is almost within normal limits. The right side contributed 47 per cent of the total oxygen consumption and 43 per cent of the total ventilation. In almost all cases where high lingulectomies are performed in conjunction with left lower lobe lobectomies the phrenic nerve is thoroughly crushed to prevent over-distention of the remaining segment of the upper lobe (figure 4). Chart 4 illustrates the bronchospirometric tracing in such

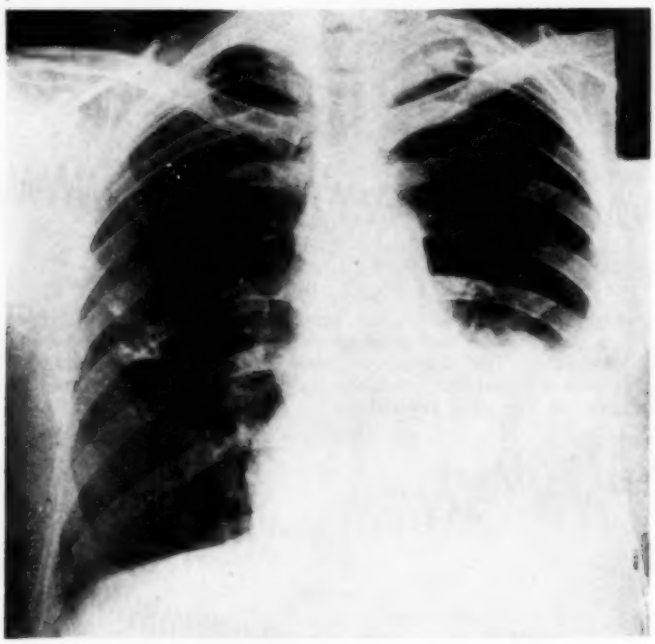

FIG. 4. Postoperative roentgenogram taken seven weeks following resection of the left lower lobe and lingula of the upper lobe. The phrenic nerve was crushed three days following operation to prevent overdistention of the remaining segment of the upper lobe.

a patient. The oxygen consumption of the upper portion of the upper lobe contributed 33.3 per cent of the total oxygen consumption and 26.3 per cent of the total ventilation. This is comparable to the amount of lung tissue remaining. In cases in which the diaphragm has been paralyzed, the ventilatory factor appeared more impaired than the efficiency of oxygen absorption.

In no instance in this group was the pulmonary function following an uneventful lobectomy significantly impaired. From the above, it is shown that the pulmonary function two to three months postoperatively on the operated side in patients with uneventful convalescence may be within normal limits. Two patients upon whom lobectomies had been performed one

and three years previously also had essentially normal bronchospirometric findings. From this one might assume that the pulmonary function on the operated side following lobectomy might remain good, but a larger series of cases should have such studies performed over a longer period of time before any definite conclusions should be reached. In patients in whom an undue degree of emphysema of the residual lobe will be necessary to obliterate the residual space, elevation of the diaphragm by phrenic nerve paralysis should be accomplished to preserve the pulmonary function. If the postoperative period is complicated by bronchopleural fistulae and infection, impaired function is to be expected.

Ten patients upon whom bronchospirometric studies were performed preoperatively showed the average oxygen consumption for the bronchiectatic side to be 37 per cent of the total and the average ventilation to be 44 per cent of the total. In addition to showing the effects of bronchiectatic

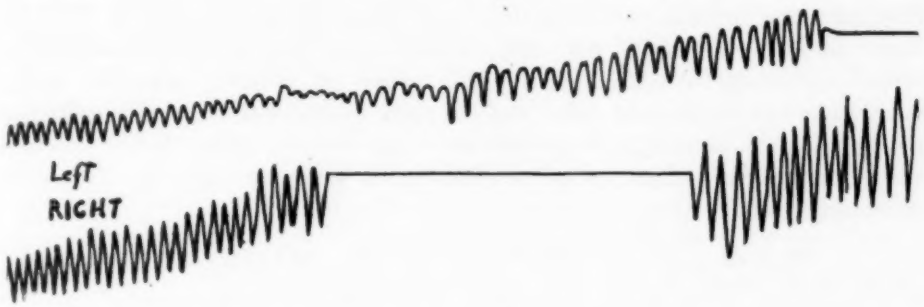


CHART IV. Bronchospirometric tracing performed seven weeks postoperatively in patient whose roentgenogram is demonstrated in figure 4. The remaining segment of the upper lobe contributed 33.3 per cent of the total oxygen consumption and 26.3 per cent of the total ventilation.

destruction on pulmonary function, this illustrates that the efficiency of oxygen absorption into the alveolar capillaries or through the alveolar membrane is more impaired than the ability to ventilate the lung. It further illustrates the inaccurate impression of pulmonary function that would be obtained from vital capacity studies alone. It is of interest to note that bronchospirometric studies performed on one patient with minimal bronchiectasis in the right lower lobe showed that this side had the better function. The oxygen consumption in the bronchiectatic side in this patient was 61.1 per cent, as compared to 38.9 per cent for the apparently good side. It is evident that in this patient destructive changes not apparent roentgenologically on bronchographically were present in the supposedly good lung. In another patient with segmental bronchiectasis of the right lower lobe, the oxygen consumption and ventilation upon that side were normal. Two patients not included in the above had such copious amounts of sputum as to cause bronchial obstruction to the extent that no oxygen absorption on the affected side took place.

From this it is apparent that the bronchiectatic lobe in many instances contributes very little to the oxygenation and gas exchange of blood circulating its pulmonary tissue; that blood returns to the heart unoxygenated and with a high carbon dioxide content. This in turn is largely responsible for the evidence of cyanosis and dyspnea seen in these patients. By removing the diseased or bronchiectatic tissue, blood can then only be circulated through alveoli that allow the proper oxygenation and diffusion of gases.

## Summary

Permanent cure in bronchiectasis can be attained only by pulmonary resection. The operative mortality and morbidity is today so small in contrast to that inherent in the disease that operation can be recommended without hesitation. The surgical management of 220 consecutive lobectomies with only one operative death is presented, an incidence of 0.4 per cent. Postoperative bronchopleural fistulae and empyemata occurred in only 20 cases, an incidence of 9.7 per cent. Pulmonary function as determined by bronchospirometric studies in a small group of patients pre- and postoperatively demonstrated that the oxygen consumption and ventilation within several months postoperatively were only slightly below normal values and in most cases either essentially the same or improved over preoperative levels.

*Note:* Since this paper was submitted for publication, 38 additional lobectomies were successfully performed.

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# LATE RESIDUALS IN PRESUMABLY CURED ACUTE INFECTIOUS HEPATITIS *

By GERALD KLATSKIN, M.D.,† *New Haven, Connecticut* and EMANUEL M. RAPPAPORT, M.D.,‡ *Jamaica, N. Y.*

RECENT epidemics of acute infectious hepatitis have been the subject of intensive investigation. Interest has been largely focused on etiology, epidemiology, pathology and treatment, and many important contributions have been made. Relatively little attention has been paid to the residuals and relapses of this disease and many questions regarding its prognosis remain unanswered.

Ninety to 95 per cent of patients with infectious hepatitis apparently recover in a period of two to three months. The clinical course in the remainder varies considerably. We have had an opportunity to study a large number of patients with infectious hepatitis, most of whom have had a prolonged course. Our interest has been focused on the factors responsible for the delayed convalescence, the occurrence of late residuals and the development of relapses.[1] In conjunction with these studies we have investigated a large number of individuals who have had infectious hepatitis in the past and who were presumably cured. The results of this investigation are the subject of this report.

A number of investigators have reported evidence of impaired liver function in a high proportion of individuals who have recovered from acute hepatitis.[2, 3, 4, 5, 6] Most of these observations have been made on small groups of patients and liver function studies have been limited to a single type, usually the bilirubin excretion test [2-4] or the level of the serum bilirubin.[5] Symptoms referable to the liver have been noted by some,[2, 4, 7] but not by others.[5, 6] Although enlargement of the liver has been present in a variable proportion of most groups,[2, 4, 5, 7] it has not been found in all.[3, 6, 8] Scant attention has been paid to the possible factors responsible for the occurrence of these late residuals, and their significance remains in doubt. Although they are compatible with good health for long periods, it has been suggested that they may be a forerunner of cirrhosis.[2, 3, 5, 7]

The purpose of this investigation has been (1) to determine the incidence of residuals in a large group of individuals presumably recovered from acute infectious hepatitis, (2) to evaluate the factors that may have played a rôle in their occurrence, and (3) to assess their clinical significance.

* Received for publication April 9, 1946.

† Department of Internal Medicine, Yale University School of Medicine. Formerly Chief of Medical Service, Schick General Hospital, Clinton, Iowa.

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## Material and Methods

Approximately 3,000 patients were surveyed by questionnaire regarding a history of jaundice in the past. After excluding cases admitted because of jaundice or its sequelae and those who, on careful questioning, did not appear to have had a definite attack, there remained a total of 217 patients with a clear-cut history of acute hepatitis with jaundice in the past. The interval between the onset of the disease and the medical survey varied from two months to 27 years.

*History.* Each of these patients was interviewed and a detailed history of his attack recorded. Emphasis was placed on the depth and duration of jaundice, the duration of bed rest, the alcohol intake, the presence of syphilis or other complicating disease, the relation of the attack to transfusions of blood or plasma or to the inoculation of yellow fever vaccine, the occurrence of relapses or reinfections and the presence of symptoms.

The depth of jaundice was recorded as mild, moderate or severe. Where the icterus index was known values up to 50 were considered mild, between 50 and 100 moderate, and over 100 severe.

Patients who developed their jaundice within two to four months of a transfusion of blood or plasma or an inoculation of yellow fever vaccine were classified as homologous serum jaundice or yellow fever vaccine jaundice respectively. Since there is no conclusive evidence to indicate that the etiology and pathology of these two forms of hepatitis are different from those of infectious hepatitis, they have been included in this study, although the residuals in each group have been considered separately. One hundred and sixty-seven patients had had infectious hepatitis, 30 homologous serum jaundice, and 20 yellow fever vaccine jaundice.

Residual symptoms were considered significant only if they were moderate to severe in degree, definitely had their onset with the attack of jaundice, had been present continuously since, and could not be attributed to any other cause present.

*Physical Examination.* The abdomen was examined carefully for evidence of liver enlargement and tenderness, splenomegaly and collateral venous circulation. The sclerae were inspected for icterus and the skin for spider nevi and palmar erythema.

The liver was considered enlarged when it could be palpated at least one finger's-breadth below the right costal margin in the mid-clavicular line and when its upper border was percussed no lower than the fifth intercostal space anteriorly. The character of the edge and its consistency were recorded. Subcostal tenderness was elicited in the usual manner, percussion tenderness by striking the fist sharply against the hand placed across the lower right chest anteriorly, and compression tenderness by the method previously described.[9]

*Liver Function Studies.* It is generally accepted that a complete appraisal of liver function cannot be attained by any single test,[10] especially

when minor degrees of impairment are present. It is necessary, therefore, to study liver function by a variety of methods. In our experience a fair estimate of liver function can be made by determining the one-minute and total serum bilirubin, the thymol turbidity and cephalin-cholesterol flocculation reactions, the bromsulfalein excretion, the quantitative urinary urobilinogen excretion, and the total serum proteins and albumin-globulin ratio. Due to conditions beyond our control it was not always possible to carry out all these studies on every patient in this investigation. The number of tests performed is enumerated in table 2. The total serum proteins and albumin-globulin ratio were determined too infrequently to be included in our results.

The fasting *one-minute serum bilirubin* [11] was considered abnormal when it was above 0.2 mg. per cent. All our normal controls fell below this level.

The fasting *total serum bilirubin* [12] was considered abnormal when it was above 1.0. mg. per cent. Our normal controls usually fell below 0.75 mg. per cent.

The Maclaglan *thymol turbidity test* [13] was considered abnormal when values of 5 or above were obtained.

*The cephalin-cholesterol flocculation test* [14] was considered abnormal when there was a minimum of 1 + flocculation in 24 hours and 2 + in 48 hours.

The *bromsulfalein excretion* was determined by measuring the retention of dye at the end of 45 minutes following the intravenous injection of 5 mg. per kilogram of body weight.[15] A retention of 6 per cent or more was considered abnormal. Normal controls rarely showed any retention. The significance of values between 1 per cent and 5 per cent will be discussed later.

The quantitative urobilinogen determination was carried out by Watson's method [16] on urines collected between 9 and 11 a.m. following the ingestion of 200 c.c. of water. A minimum of three specimens was studied. If two of the three specimens contained more than 1.2 units it was considered as evidence of impaired liver function. In our experience normals usually excrete less than 1.0 unit, but a few excrete between 1.0 and 1.2 units in two hours, so that we have eliminated all border-line values in this study.

*Statistical Analysis.* All data included in the tables that follow have been subjected to statistical analysis by the Chi-Square Test. Differences between groups were considered significant only when $X^2 = 6.0+$; $n = 1$; $P < 0.015$.*

## Results

One hundred and eight of our 217 cases (50 per cent) of presumably cured infectious hepatitis had symptoms referable to the liver, hepatomegaly or evidence of impaired liver function. Forty-seven (22 per cent) had

* The authors are indebted to Dr. Alexander W. Winkler, Yale University School of Medicine, for his assistance in analyzing our data.

symptoms, 59 (27 per cent) had hepatomegaly and 41 (19 per cent) had evidence of impaired liver function. There was considerable overlapping of these residuals, so that one-third of the patients had two or more of the three groups of residuals (table 1). There did not appear to be any significant relationship between the incidence of residuals and the time elapsed since the onset of hepatitis (tables 1 and 2).

*Symptoms.* A great variety of symptoms have been attributed to the liver with residual damage following an attack of acute hepatitis.[2] After careful analysis of our data we found that only two symptoms could be considered significant—fat intolerance and pain (table 2). The other symptoms elicited could not be traced to the attack of jaundice and very frequently other factors played a rôle in their inception. As already indicated only moderate or severe degrees of discomfort were considered significant.

TABLE I

Relation of Residual Symptoms, Hepatomegaly and Impaired Function to the Interval Since the Onset of Jaundice in 217 Cases of Presumably Cured Infectious Hepatitis

| | Total Cases | Interval | | | |
|---|---|---|---|---|---|
| | | 2–4 mos. | 5–12 mos. | 1–4 yrs. | 5–27 yrs. |
| *Hepatomegaly* | *59* (27%) | *9* | *16* | *27* | *7* |
| With symptoms | 12 | 1 | 5 | 5 | 1 |
| With impaired function | 7 | 1 | 2 | 4 | 0 |
| With symptoms and impaired function | 9 | 0 | 4 | 5 | 0 |
| *Symptoms* | *47* (22%) | *4* | *26* | *16* | *1* |
| With hepatomegaly | 12 | 1 | 5 | 5 | 1 |
| With impaired function | 2 | 1 | 0 | 1 | 0 |
| With hepatomegaly and impaired function | 9 | 0 | 4 | 5 | 0 |
| *Impaired Liver Function* | *41* (19%) | *6* | *11* | *18* | *6* |
| With hepatomegaly | 7 | 1 | 2 | 4 | 0 |
| With symptoms | 2 | 1 | 0 | 1 | 0 |
| With hepatomegaly and symptoms | 9 | 0 | 4 | 5 | 0 |
| *Hepatomegaly, Symptoms or Impaired Liver Function* | *108* (50%) | *16* | *38* | *41* | *13* |

*Fat intolerance* was by far the most striking symptom and occurred in 44 of the 51 patients with symptoms. The intolerance was almost invariably limited to fried foods and pork and rarely extended to the bland fats of milk, butter and eggs. It was usually manifested by vague discomfort or pain, bloating and eructations shortly after eating.

*Pain* occurred in 18 cases. In most of these it was associated with fat intolerance and was poorly localized in the right upper quadrant and epigastrium. In the others it appeared to be related to tenderness of the liver and was precipitated by deep breathing, bending, twisting and jarring. As a rule it was aching in character and was never colicky.

Twenty-three of the 47 cases with symptoms had enlargement of the liver, evidence of impaired liver function or both (table 1).

*Physical Findings.* Significant *enlargement of the liver* was found in 59 of the 217 cases studied. Twenty-eight of these had associated symptoms, or impaired liver function or both (table 1). In addition, there were 34 patients with borderline enlargement of the liver. Some of these were probably significant, since they were associated with symptoms or impaired function, but they have been excluded from consideration.

Thirty-six of the 59 enlarged livers exhibited mild to moderate percussion tenderness. Subcostal and compression tenderness occurred much less frequently (table 2). A large number of patients had percussion, subcostal or compression tenderness of mild degree without hepatomegaly. Although some of these may have been of significance, especially when there was evidence of impaired liver function, they have been excluded from consideration.

TABLE II

Residuals Found in Presumably Cured Acute Infectious Hepatitis

| | Total (217 cases) | Interval Since Onset of Hepatitis | | | |
|---|---|---|---|---|---|
| | | 2–4 mos. (32 cases) | 5–12 mos. (72 cases) | 1–5 yrs. (81 cases) | 5–27 yrs. (32 cases) |
| *Symptoms* | | | | | |
| Fat intolerance | 44 (18%) | 4 | 23 | 16 | 1 |
| Pain | 18 ( 8%) | 1 | 11 | 6 | 0 |
| *Physical Findings* | | | | | |
| Hepatomegaly | 59 (27%) | 9 | 16 | 27 | 7 |
| With percussion tenderness | 36 | 6 | 10 | 17 | 3 |
| With local tenderness | 16 | 3 | 4 | 7 | 2 |
| With compression tenderness | 8 | 1 | 0 | 5 | 2 |
| Splenomegaly | 7 ( 3%) | 2 | 3 | 2 | 0 |
| *Impaired Function* | | | | | |
| Serum bilirubin | | | | | |
| One minute | 2 ( 1%)† | 1 (30)* | 0 (61)* | 1 (66)* | 0 (32)* |
| Total | 9 ( 4%)† | 2 (32)* | 1 (72)* | 4 (80)* | 2 (32)* |
| Thymol turbidity | 7 ( 4%)† | 1 (30)* | 1 (61)* | 3 (57)* | 2 (31)* |
| Cephalin-cholesterol | 12 (11%)† | 1 (11)* | 5 (46)* | 4 (42)* | 2 (10)* |
| Bromsulfalein | 15 (11%)† | 2 (18)* | 4 (39)* | 9 (65)* | 0 (20)* |
| Urobilinogen | 17 (13%)† | 4 (13)* | 5 (44)* | 7 (62)* | 1 (15)* |

* Number of tests performed.
† Per cent of total number of tests performed.

The enlarged liver usually had a sharp, soft, easily palpable edge, but in six the edge was described as round and soft, and in three as sharp and firm. The latter will be discussed later.

An *enlarged spleen* was palpated in seven patients. All had one or more residuals of hepatitis, including six with symptoms, five with hepatomegaly and three with impaired liver function. Although none had had attacks of malaria, four had seen service in malarious areas and had taken suppressive atabrine therapy.

One patient exhibited faint scleral icterus in association with an enlarged, non-tender liver, but his one-minute and total serum bilirubin levels were normal, so that the finding was not considered significant.

One patient with borderline enlargement of the liver had prominent veins over the abdominal wall and chest, but there was no evidence of ascites or impaired liver function.

Typical spider nevi were demonstrated on the chest of one case, but they were not considered significant because their appearance antedated the jaundice by a considerable period and there were no evidences of liver damage.

Palmar erythema was not found in any of our cases.

*Liver Function Tests.* Forty-one cases (19 per cent) had evidence of impaired liver function. In 31 of these impairment was demonstrated by two or more tests (table 3). Residual symptoms, hepatomegaly or both were present in 18 (table 1).

TABLE III

Confirmatory Evidence of Liver Damage with Tests Indicating Impaired Liver Function

| | No. of Abnormal Tests | Other Abnormal Tests | Hepatomegaly | Symptoms | None |
|---|---|---|---|---|---|
| 1 min. bilirubin | 2 | 2 | 0 | 0 | 0 |
| Total bilirubin | 9 | 5 | 3 | 3 | 3 |
| Thymol turbidity | 7 | 2 | 1 | 1 | 4 |
| Cephalin-cholesterol flocculation | 12 | 4 | 4 | 4 | 8 |
| Bromsulfalein | 15 | 9 | 11 | 9 | 2 |
| Urobilinogen | 17 | 9 | 9 | 8 | 4 |

There did not appear to be any significant difference in the time intervals during which the various tests were capable of demonstrating impaired liver function (table 2) and no one test was found to be significantly superior to the others (tables 2 and 3).

In general, the degree of impaired function revealed by our tests was mild. The following are the average and range of abnormal values we found:

| | Average | Range |
|---|---|---|
| 1 minute serum bilirubin | 0.54 mg. % | 0.50–0.57 mg. % |
| Total serum bilirubin | 1.32 mg. % | 1.05–2.20 mg. % |
| Thymol turbidity | 5.8 | 5–7 |
| Cephalin-cholesterol flocculation | 1+/2+ | 1+/2+–2+/3+ |
| Bromsulfalein retention | 9% | 6.7–18% |
| Urobilinogen (2 hour) | 1.73 units | 1.44–2.44 units |

Although we have considered bromsulfalein retention up to 6 per cent at the end of 45 minutes normal, to exclude all borderline cases in this study, a comparison of the group showing retention between 1 per cent and 6 per cent with the one with retention over 6 per cent suggests that the former is equally significant as an index of impaired liver function (table 4).

TABLE IV

Comparison of Confirmatory Evidence of Liver Damage with Bromsulfalein Retention of 1 to 5 per cent and over 6 per cent (45 minutes, 5 mg. per kg.)

| Bromsulfalein retention | No. Cases | Confirmatory Evidence of Liver Damage | | | |
|---|---|---|---|---|---|
| | | Any Residuals* | Other Abnormal Function Tests | Hepatomegaly | Symptoms |
| 1 to 5 per cent | 37 | 20 (54%) | 6 | 10 | 10 |
| 6 per cent and over | 15 | 13 (87%) | 10 | 11 | 8 |

* Hepatomegaly, impaired liver function or symptoms.

*Factors Influencing the Occurrence of Residuals.* The duration and severity of jaundice appeared to be the only two factors which bore any relation to the incidence of residuals (table 5). The patients with severe jaundice had a significantly higher incidence of residuals than the others. The apparent influence of the duration of jaundice, however, was probably related to the fact that jaundice lasted longer when it was severe. Eleven (73 per cent) of the 15 cases with jaundice of eight or more weeks' duration, and only 32 (16 per cent) of the 201 cases of shorter duration were classified as severe.

The type of hepatitis, age, alcohol consumption and syphilis were insignificant factors in the occurrence of residuals.

In view of the recognized influence of inadequate bed rest on the occurrence of recrudescences during the convalescent stage of hepatitis [17, 18] an attempt was made to study its effect on the appearance of late residuals. There was no significant difference between those who had been kept in bed for the entire duration of their jaundice or longer, and those who had had bed rest for less than the duration of jaundice.

It seemed reasonable to suppose that the additive effects of multiple attacks of jaundice would increase the incidence of residuals, but there was no statistically significant difference between the groups with and without recurrences.

The nature of these recurrences was difficult to interpret. Of the 21 patients with a single recurrence, 11 had had it under two years and 10 had had it over two years following the initial attack. Five patients had had two or more recurrences at intervals between one month and 12 years. The interval between these recurrences was under two years in six and over two years in the remaining six. Obviously, then, it was impossible to differentiate relapses from reinfections. The problem became even more difficult when the type of jaundice was considered. The history suggested that three patients had had both infectious hepatitis and yellow fever vaccine jaundice, one patient infectious hepatitis and homologous serum jaundice and one patient infectious hepatitis following an arsenotoxic hepatitis. In each of these cases the interval between the attacks had been well over two years and

TABLE V

Possible Factors in the Incidence of Residuals in Presumably Cured Acute Infectious Hepatitis

| | No. Cases* | Hepatomegaly, Symptoms or Impaired Function | Hepato-megaly | Symptoms | Impaired Liver Function |
|---|---|---|---|---|---|
| *Type of hepatitis* | | | | | |
| Infectious | 167 | 87 (52%) | 48 | 35 | 35 |
| Homologous serum | 30 | 13 (43%) | 5 | 7 | 4 |
| Yellow fever vaccine | 20 | 8 (40%) | 6 | 5 | 2 |
| *Severity of jaundice* | | | | | |
| Mild and moderate | 169 | 74 (44%) | 36 | 19 | 24 |
| Severe | 43 | 32 (74%) | 21 | 17 | 15 |
| *Duration of jaundice* | | | | | |
| Less than 8 wks. | 197 | 94 (48%) | 50 | 41 | 33 |
| Over 8 wks. | 15 | 12 (80%) | 7 | 5 | 6 |
| *Bed rest* | | | | | |
| Less than jaundice | 107 | 59 (55%) | 31 | 20 | 22 |
| Duration of jaundice or longer | 70 | 35 (50%) | 14 | 16 | 11 |
| *Recurrences of jaundice* | | | | | |
| None | 191 | 91 (47%) | 46 | 35 | 34 |
| One or more | 26 | 17 (65%) | 13 | 13 | 7 |
| *Age* | | | | | |
| Under 35 yrs. | 204 | 99 (49%) | 55 | 44 | 37 |
| Over 35 yrs. | 13 | 9 (69%) | 4 | 3 | 4 |
| *Alcohol consumption* | | | | | |
| None or little | 128 | 60 (47%) | 30 | 25 | 24 |
| Moderate or heavy | 54 | 27 (50%) | 17 | 7 | 8 |
| *Syphilis* | | | | | |
| Syphilitics | 6 | 1 (17%) | 1 | 0 | 0 |
| Non-syphilitics | 211 | 107 (51%) | 58 | 47 | 41 |
| *Malnutrition* | | | | | |
| Prisoners of war | 43 | 23 (53%) | 10 | 5 | 9 |
| Non-prisoners | 174 | 85 (49%) | 49 | 42 | 32 |
| *Geographical*† | | | | | |
| U.S.A. | 43 | 19 (44%) | 12 | 5 | 10 |
| E.T.O. | 83 | 37 (45%) | 17 | 20 | 9 |
| S.W.P. | 72 | 40 (56%) | 21 | 14 | 21 |
| Mediterranean | 19 | 11 (58%) | 8 | 7 | 2 |

* Total number of cases was 217, but data were incomplete in some groups, which accounts for differences in totals noted in this column.

† Where disease was contracted. U.S.A.—includes a few cases from Hawaii and Alaska. E.T.O.—Europe, excluding Italy. S.W.P.—Islands of Southern and Central Western Pacific Ocean. Mediterranean—Italy and North Africa.

the clinical and epidemiologic history suggested reinfection rather than relapse.

In six of the 26 recurrent cases (23 per cent) and in 37 of the 186 non-recurrent cases (19 per cent) the jaundice had been severe, so that there did not appear to be any significant relationship between recurrences and the severity of jaundice.

The recent interest in dietary factors in liver injury [19] led us to examine this problem. Forty-three of our cases had been prisoners of war for periods of one to three years, chiefly in the Philippines and Japan. They had all suffered severe malnutrition, complicated almost invariably by beriberi and frequently by pellagra and scurvy. A comparison of this group with the non-prisoners failed to disclose any significant difference in the incidence of hepatic residuals.

To evaluate the possibility that differences in the virulence of the infecting agent might have played a rôle in determining the incidence of residuals, the cases from each of the major Theaters of Operation and the United States were compared. No significant differences were noted.

Recently it has been pointed out that atabrine, given over a long period in the suppressive treatment of malaria, may cause serious liver disease in a few susceptible individuals.[20] The patients from the Southwest Pacific and Mediterranean Theaters of Operation, where suppressive treatment with atabrine was routine, were compared with those from the European Theater and the United States, and no significant difference in the incidence of residuals could be demonstrated.

## Discussion

One half of our 217 patients, who were considered fully recovered from acute infectious hepatitis, had residuals evidenced by symptoms, hepatomegaly, or impaired liver function, for periods ranging up to 27 years. Others [3, 4, 6] have found an even higher incidence of residuals and there is good reason to believe that a higher incidence would have been found in this series had a greater variety and number of liver function tests been performed. Our results have not been weighted by a large number of patients who might be considered convalescent. Only 32 in the series had had their jaundice within a four month period.

The symptoms described appeared to be related to some disturbance of the liver. In every instance they could be traced to the attack of jaundice, no other etiology could be found and in approximately one-half the patients they were associated with hepatomegaly and/or impaired liver function. Recently several workers [8, 21] have denied the relationship of these symptoms to liver damage and have indicated that they are psychogenic in origin. All their cases had been hospitalized for a long time and had never fully recovered, so that they can not be compared with our cases. Moreover, psychogenic factors could hardly have played a rôle in our group, since none of the patients had sought medical attention or lost time from duty because of these symptoms, even though they were moderate to severe in degree. It is noteworthy that in one of the reports [21] an appreciable number of the patients with psychogenic factors had hepatomegaly and impairment of liver function. Kalk,[2] who believes these symptoms are due to liver disease, has commented on the fact that the clinical syndrome frequently simulates psychoneurosis.

Hepatomegaly was the most common residual in our series. Our criteria for pathological enlargement of the liver were sufficiently rigid to exclude the occasional normally palpable liver in thin individuals with narrow costal angles. Moreover, the significance of our findings was enhanced by the appreciable number that were associated with tenderness and impaired function. Most other investigators [2, 4, 5, 7] have found hepatomegaly in an appreciable number of patients presumably cured of acute hepatitis, but have demonstrated that hepatomegaly and impaired function do not always go hand in hand,[5, 21] as was also true in the present investigation.

Impairment of liver function appears to be the most common residual reported in the literature,[3-6] whereas it was the least common in our series. This is probably related to the use of the bilirubin excretion test which is more sensitive than any of those we employed.

That the severity of the jaundice played a rôle in the occurrence of residuals was to be expected, although the relationship has not been noted by some.[3] We were greatly surprised, however, to find that bed rest and recurrences were insignificant factors, since in our experience with active hepatitis they proved to be very important.[1]

Polack [7] believes that inadequate treatment of an acute attack of infectious hepatitis predisposes to the development of chronic hepatitis, a syndrome not unlike those of our cases with residuals and recurrences. Our data did not permit evaluation of this possibility.

Barker,[18] in a recent report, has described a group of patients with persistent symptoms, signs and impaired function following an attack of acute hepatitis, who characteristically relapse when exercised. He believes these are examples of chronic active infection of the liver. None of our cases exhibited this tendency to relapse after exercise, although the clinical picture in many resembled "Chronic Infectious Hepatitis." We have, however, seen the typical syndrome in a number of our active cases with delayed convalescence.[1] Whether the infective agent is actually present in the liver remains to be demonstrated.

The question of whether the residuals described are due to structural changes in the liver remains unanswered, since no biopsies were performed.

There is ample evidence that impaired function may occur in the absence of gross or microscopic changes in the liver, as, for example, demonstrated by its failure to inactivate estrogen when injured by vitamin B-deficient diets.[22] Also, hepatomegaly in the post-hepatitis syndrome may occur in the absence of histologic changes, as illustrated by the two negative biopsies reported by Benjamin and Hoyt.[21] Nevertheless, periportal fibrosis, cellular infiltration, proliferation of the bile ducts and distortion of the lobules have been found in some clinically cured cases of hepatitis.[23, 24] How long these structural changes may persist has not been determined, although some have been demonstrated as long as four months after apparent clinical cure.[24] Unfortunately in neither of the recent reports on biopsy and autopsy material [23, 24] were data available on the status of the liver function, so that

its relation to structural changes could not be determined. In our three cases with enlarged firm livers, two of which were tender, and one of which was associated with impaired function, it seems reasonable to suppose that structural changes had occurred.

There is considerable debate over the question of whether infectious hepatitis may go on to cirrhosis. Most workers in the field agree that the vast majority of non-fatal cases go on to clinical recovery, that a variable proportion of these have residuals which are compatible with good health, but that occasionally the latter are progressive and result in cirrhosis.[2, 3, 5, 7, 23] Lucké [24] defends the view that restoration of structure is always complete, and that cirrhosis never occurs. He believes that the cases reported in which scarring was demonstrated either had it before the onset of hepatitis or suffered a form of liver disease other than infectious hepatitis.

Some of these divergent views appear to stem from differences in terminology. In the case of epidemic hepatitis presented by Dible,[23] which went on to what he termed "cirrhosis," there was nodular hyperplasia, bile-duct proliferation and fibrosis of the portal tracts. A number of Lucké's [25] fatal cases exhibited identical findings, but the appearance of the periportal areas was interpreted as dense compression of the reticulum fibers rather than fibrosis. Since he could find no diffuse scarring or evidence of progressive destruction of tissue, Lucké refused to consider the condition cirrhosis. Furthermore, in appraising his findings in non-fatal cases he failed to take into account the possibility that patients with lesions similar to those in his fatal group might survive, in which case complete restoration of parenchyma could hardly be claimed.

Whether the term "cirrhosis" should be applied to nodular hyperplasia with fibrosis, or reticulum condensation, is debatable if the rigid criteria of Karsner [26] are accepted. Certainly the term "coarsely nodular cirrhosis" is widely used and understood and appears to be applicable to cases like Dible's and our own.[1] It is difficult to prove that the fibrosis is progressive in these cases, but the clinical course has been identical with those seen in other forms of cirrhosis. Some have shown a progressive deterioration of liver function with jaundice, ascites and splenomegaly, while others have run an intermittent course with periods of remission of variable duration.

Himsworth and Glynn [27] have pointed out some fundamental differences in the etiology, pathogenesis and morphology of experimental portal cirrhosis and the scarring and nodular hyperplasia that supervene on the massive necrosis of the liver induced by trophic disturbances. They suggest that the massive necrosis seen in some cases of infectious hepatitis is due to trophic disturbances and that this form of necrosis always leads to scarring and nodular hyperplasia in non-fatal cases.

We have seen both nodular and portal cirrhosis following hepatitis.[1] In reviewing these cases, however, we found that in no instance of proved Laennec's cirrhosis could we unequivocally establish a diagnosis of acute infectious hepatitis at the onset of the disease, and in many there were features

to suggest that the cirrhosis antedated the onset of jaundice, which had been interpreted as infectious hepatitis. In the case of nodular cirrhosis, however, the clinical data and sequence of events clearly indicated that the cirrhosis was a sequel of infectious hepatitis.

In brief, then, there is evidence to support the view that infectious hepatitis occasionally leads to nodular cirrhosis, but rarely, if ever, to portal cirrhosis.

In connection with the present investigation we are faced with the question of whether the late residuals we have described may lead to cirrhosis, as suggested by some.[2, 3, 5, 7, 23] Our data indicate that if this occurs at all it must be rare, since no unequivocal cases of cirrhosis were discovered in the 108 cases with late residuals. There was insufficient corroborative evidence in the three cases with firm smooth livers to warrant a diagnosis of cirrhosis. Obviously a survey of this sort has the inherent weakness of dealing with a select group, from which individuals with significant defects have been excluded.

Kalk [2] has found the liver with the late residuals of hepatitis unusually susceptible to new toxic insults, and believes they may be responsible for the development of cirrhosis. If recurrences of jaundice may be regarded as new insults to the liver, they did play a rôle in the development of nodular cirrhosis early in the course of infectious hepatitis,[1] but they led neither to cirrhosis nor to an increase in residuals late in the disease. In our experience nodular cirrhosis has not developed after the first six months following an attack of acute hepatitis. It is noteworthy that of the 33 relapses in this series only seven occurred within six months of an attack of jaundice, while every recurrence in our series of nodular hyperplasia occurred in less than three months. Apparently the time element is very important in determining the susceptibility of the liver to a second injury. If sufficient time has elapsed the susceptibility may be normal, even if complete structural and functional restoration has not taken place.

## Summary and Conclusions

1. One hundred and eight of 217 patients, who were considered fully recovered from acute infectious hepatitis, had residuals evidenced by symptoms, hepatomegaly or impaired liver function for periods ranging up to 27 years.

2. The only significant symptoms were fat intolerance and right upper quadrant pain.

3. There was evidence that these residuals indicated a disturbance of the liver, but the presence of structural changes was not established.

4. The residuals were compatible with good health and full activity over long periods of time.

5. The only factor which appeared to play a significant rôle in the incidence of residuals was the severity of the jaundice.

6. There was no conclusive evidence that the late residuals described predispose the liver to further injury by recurrent attacks of jaundice or other insults. This was in striking contrast to the findings early in the course of infectious hepatitis. The significance of the interval between the initial attack and the recurrence was stressed.

7. There was no evidence to indicate that the late residuals of infectious hepatitis progress to cirrhosis. Coarse nodular cirrhosis does occur occasionally during the first six months of chronic progressive or recurrent infectious hepatitis.

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# RESIDUAL MUSTARD GAS BRONCHITIS: EFFECTS OF PROLONGED EXPOSURE TO LOW CONCENTRATIONS OF MUSTARD GAS*

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THE toxic effects of mustard vapor on the respiratory tract have been well known since July 1917, when the Germans first used this gas against the Allies. Gilchrist and Matz have described the residual effects in American soldiers eight to ten years after acute mustard gassing.

Less widely known is the fact that many persons employed in the handling of mustard gas and exposed to small quantities of the vapor over a prolonged period of time may sustain damage to the respiratory mucosa which may leave them partially or totally disabled. This statement is based on two and one half years of observation in the medical department of an industrial plant where over 200 patients have been treated for both the acute symptoms and the residual effects of mustard gas exposure.

Briefly, the evolution of chronic mustard bronchitis may be traced as follows:

A young white male previously engaged in farming or some other non-industrial occupation with no history of any previous chronic lung disease goes to work on the mustard filling line. There is a varying concentration of mustard vapor in the air during a good part of the working day. After a period of time ranging anywhere from three weeks to six or 12 months he begins to show signs of definite irritation of the conjunctival and respiratory mucous membranes. He develops some or all of the following symptoms: "red eyes," photophobia, lacrimation, impaired vision, blepharospasm; loss of taste and smell sensation, nose bleeds, sore throat, difficulty in swallowing, hoarseness, chest pain, retrosternal soreness, wheezing, and dyspnea. In addition there may be anorexia, vomiting, weight loss, general weakness, insomnia, and irritability. He is seen in the Out-Patient Department where he is given symptomatic treatment and perhaps several days sick leave or temporary transfer to another department. His condition improves somewhat and he returns to work in mustard only to have a recurrence or aggravation of his symptoms in several days or weeks. After a number of such episodes it becomes apparent that this man is not suitable for work in mustard and he is transferred out to another department, preferably one where he is free of contact with any toxic fumes or dust.

After removal from mustard his eyes and throat gradually heal. The conjunctivitis recedes, the vision returns to normal. The sore throat and

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hoarseness subside. The sense of taste returns but the sense of smell may remain impaired. The appetite improves. He may regain some of the weight he has lost and his general condition is better. But he is troubled by a persistent hacking cough which comes in paroxysms. It is most common in the morning but also occurs on lying down at night. It is often precipitated by physical exertion or when the man walks from a cold into a warm room or comes into contact with fumes or smoke. The cough is productive of anywhere from a teaspoonful to a cupful of white or yellow mucoid or mucopurulent sputum which may have a foul odor on occasion. There may be a troublesome wheezing and chest tightness most marked during damp weather. The patient seems to be more susceptible to respiratory infections than he was prior to exposure to mustard and the infections tend to last longer. He may note an afternoon temperature elevation of one to two degrees. Definite clinical bronchiectasis may develop as a result of repeated attacks of acute infectious bronchitis. He is hypersensitive to fumes and dust of any kind. He may develop dyspnea on slight or moderate exertion and therefore cannot perform any arduous labor.

Physical examination of the patient at this stage will usually reveal a fairly well-nourished individual who does not appear ill. Positive physical findings are confined to the chest which shows scattered wheezes and rhonchi over both lungs with occasional moist râles at the bases. Roentgenographic findings may range all the way from minimal increase in the prominence of the bronchovascular markings to definite peribronchial thickening and patchy basal pneumonitis. Lipiodol studies may show a normal bronchial tree or early bronchiectasis. Blood counts, blood serology, and urinalysis are usually negative. Repeated sputum examinations fail to reveal tubercle bacilli and usually show a predominance of gram positive cocci. The sedimentation rate is normal or slightly elevated. Vital capacity is somewhat diminished.

A few illustrative cases will clarify the picture of residual mustard bronchitis:

*Case 1.* J. T. O., 36 year old white male, construction steel worker. Past medical history is essentially negative. He first began work training painters in a mustard filling plant in August 1942. He was first treated at the Out-Patient Department in November 1942 because of red eye, sore throat, and hoarseness. His throat and larynx improved somewhat but his eyes continued to be red with excessive burning and tearing and some impairment of vision for which he was seen again several times in the Out-Patient Department in December 1942. On January 20, 1943 he was admitted to the Station Hospital with a diagnosis of mustard gas conjunctivitis, pharyngitis, laryngitis, and tracheobronchitis. His symptoms at that time were red eyes, photophobia, blurred vision, sore throat, dysphagia, cough, and chest pain. He had lost his taste sense, appetite was poor and he often vomited after coughing. He had lost 26 pounds in three months. He had frequent headaches and was very nervous and irritable. He slept little because of almost continual cough. Physical examination at this time showed scattered moist râles in both lungs. Pulse was 96; blood pressure was 122 mm. Hg systolic and 78 mm. diastolic; red blood cells 4,980,000; hemoglobin 14.4 grams; white blood cells 7,350, with a normal differential count. Roentgenograms

showed minimal increase in the bronchovascular markings, right lower lobe. Patient ran a low-grade spiking temperature between 98 and 100°, which gradually settled down to normal. He was discharged improved after 10 days in the hospital.

On July 20, 1943 he left the Arsenal. He stated that his chest was sore from almost continual coughing. Physical examination at that time revealed scattered rhonchi over the right chest. Temperature was 98.6°, pulse was 96, blood pressure was 112 mm. Hg systolic, 70 mm. diastolic. Following his resignation from the

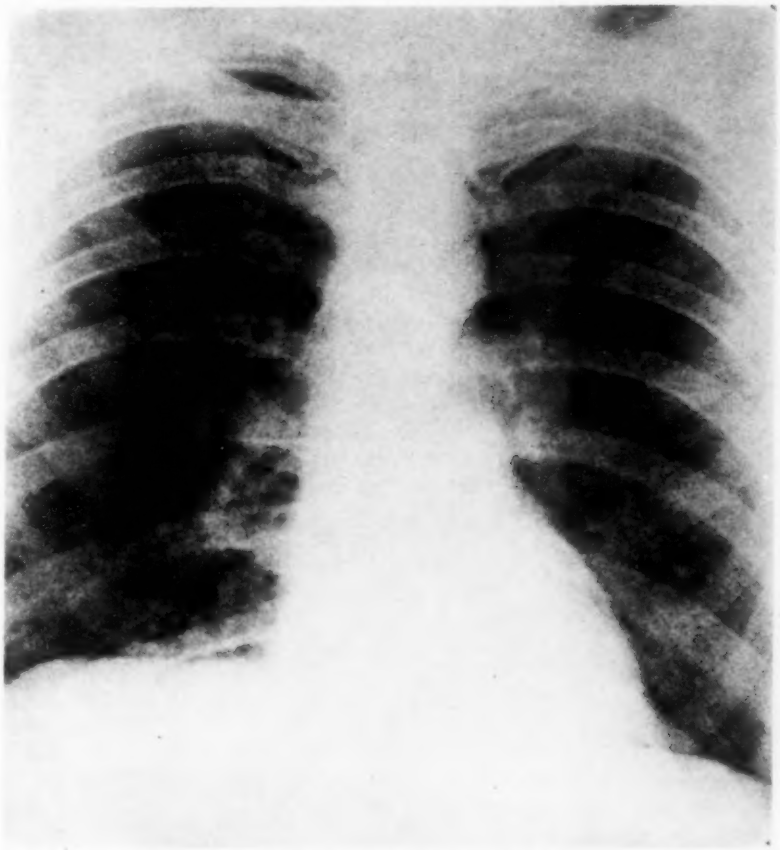

FIG. 1. Demonstrating the limitations of ordinary chest roentgenogram in chronic chemical bronchitis. J. J. L., 30 yr. old white male, worked in mustard for 20 months. Diagnosis: chronic mustard bronchitis. Has severe productive cough, dyspnea. Physical examination showed numerous rhonchi and wheezes in both lungs, vital capacity 3000 c.c., yet plain chest film is practically normal.

Arsenal he left Alabama and went out to the northwest coast to work in construction steel. His eyes and throat cleared completely within several weeks after removal from the mustard fumes. However, he found that he continued to have a paroxysmal cough productive of about one-fourth cupful of white or yellowish mucoid sputum. The cough would often start when he became overheated or exerted himself. He found that he tired easily and finally had to leave the northwest coast because of the excessive dampness which made his chest feel tight and increased his wheezing.

He returned to Alabama in February 1945 and was hospitalized February 28, 1945 because of his persistent cough. Physical examination at this time revealed

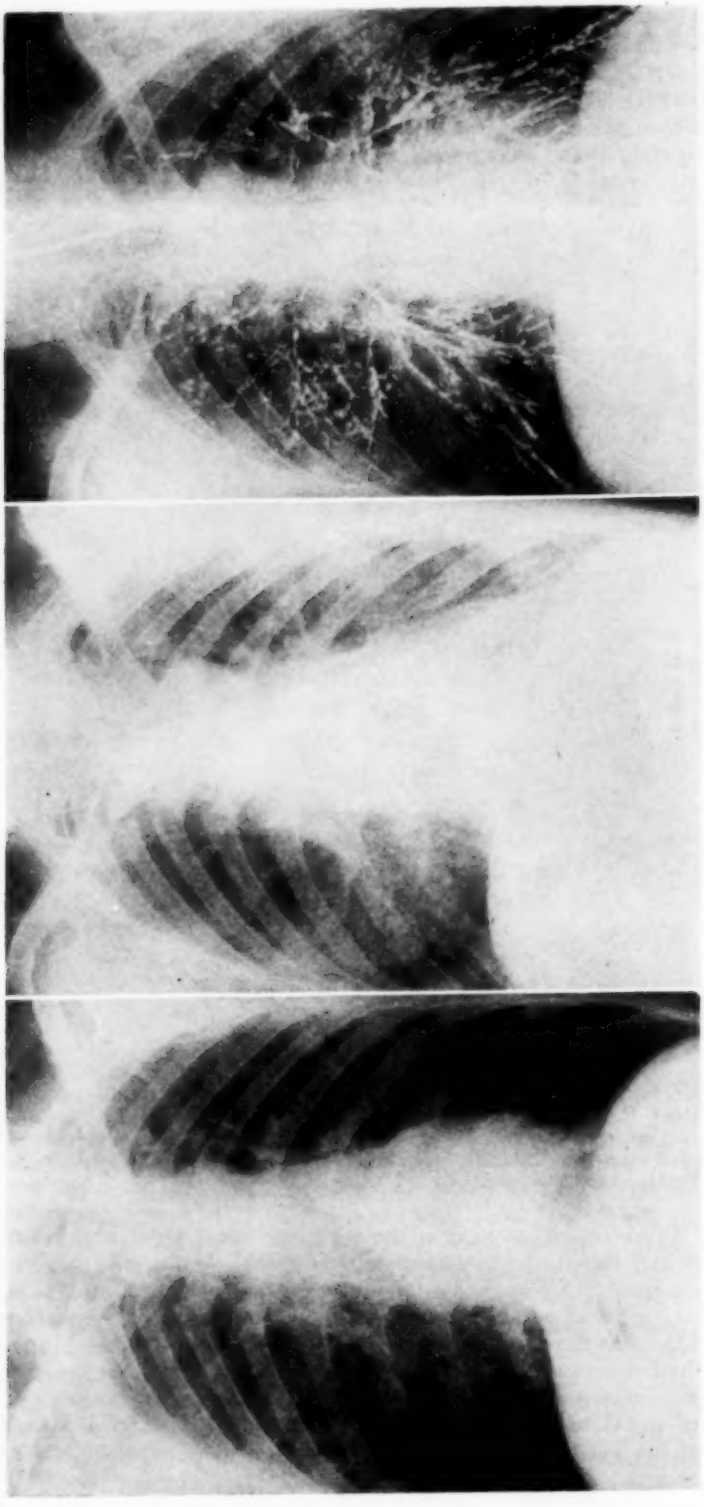

FIG. 2. J. L. C., 46 yr. old white male, worked in mustard from December 1942 to July 1943. Complained of residual cough, wheezing, and chest tightness. Film of June 15, 1943 normal except for minimal increase in the bronchovascular markings, right lower lobe. Left base is clear. Film of February 24, 1945 shows fibrosis at left base in addition to increased markings, right lower lobe. Lipiodol studies March 7, 1945 show minimal bronchiectasis, left lower lobe.

scattered rhonchi and moist râles over the entire right lung. There were a few moist râles also at the left base. Blood pressure 140 mm. Hg systolic and 80 mm. diastolic; vital capacity 3500 c.c.; sputum was negative for acid-fast bacilli and showed a predominance of gram positive cocci; urinalysis was negative; red blood cells 4,500,000; 83 per cent hemoglobin; white blood cells 9,800 with 74 per cent neutrophiles, 24 per cent lymphocytes, 1 per cent monocytes, 1 per cent eosinophiles; sedimentation rate 10 mm. in one hour. Roentgenograms showed slightly increased prominence of the bronchovascular markings in the lower half of the right lung. Lipiodol studies revealed minimal fusiform bronchiectasis in the right lower lobe. Treatment consisted of postural drainage four times a day; ammonium chloride, grains 15, four times a day; high fluid intake and a high vitamin diet. His cough diminished somewhat and his sputum decreased. He was discharged home improved after 10 days in the hospital. He was seen in the Out-Patient Department on April 17, 1945, and stated that he had just been forced to quit work with a construction company because he tired too easily and could not complete the required 10-hour working day. He still has intermittent cough productive of one to three teaspoonfuls of yellowish mucoid sputum.

*Case 2.* G. C. R., a 33 year old white male; formerly worked as a farmer. Past medical history essentially negative. He was hired as an assembly operator in a mustard filling plant in August 1942. He first developed cough in October 1942. He was seen in the Out-Patient Department three times in November 1942 because of mustard gas conjunctivitis and tracheobronchitis. He was also treated several times in January 1943 because of cough, chest pain, smothering sensations, and anorexia, and he was given seven days sick leave. His symptoms persisted and he was admitted to the Station Hospital March 19, 1943. In addition to his cough which was worse at night, he also gave symptoms of paresthesia and anesthesia of the face. Physical examination on admission showed diminished breath sounds at both bases, posteriorly, with inconstant coarse râles and wheezes at the right base. Blood pressure was 96 mm. Hg systolic and 60 mm. diastolic; pulse 92; temperature 99.4°; urinalysis and test for syphilis were negative. On symptomatic treatment patient's temperature dropped to normal. After several days the cough lessened. He was discharged back to work on April 2, 1943 at which time he had only a few inconstant râles at the right base. A roentgenogram at this time showed slight peribronchial thickening at the basal portion of the left lung.

On April 23, 1943 he was seen again in the Out-Patient Department. He stated that he had gained a few pounds in weight but he still had cough productive of considerable amounts of yellow sputum. On May 10, 1943 he was again hospitalized because of cough productive of about one teaspoonful of yellowish white mucoid sputum. He had also had dyspnea on moderate exertion, tight sensation in chest, worse in cloudy or damp weather, and night sweats. His temperature was normal. Physical examination showed coarse râles at both bases, more marked on the right side. Red blood cells were 4,350,000; hemoglobin 75 per cent; white blood cells 12,450 with 82 per cent neutrophiles, 14 per cent lymphocytes, and 4 per cent eosinophiles. Urinalysis was negative. Patient was treated symptomatically and was discharged, improved, on May 20, 1943. He was granted one month's sick leave. He was seen again in the Out-Patient Department on June 21, 1943, at which time he complained of his cough having been worse in the past two weeks. He claimed that he raised small amounts of foul yellowish sputum particularly in the morning. He also had anorexia, morning nausea, weakness, paroxysmal cough, and substernal soreness. Physical examination revealed fine and coarse râles throughout both lungs. Sedimentation rate was 28 mm.

He was sent to a veteran's hospital on August 5, 1943, for evaluation of his chest conditions, but he refused to stay for adequate examination. He returned to work taking lids off boxes in October 1943. He continued to work in the box factory until

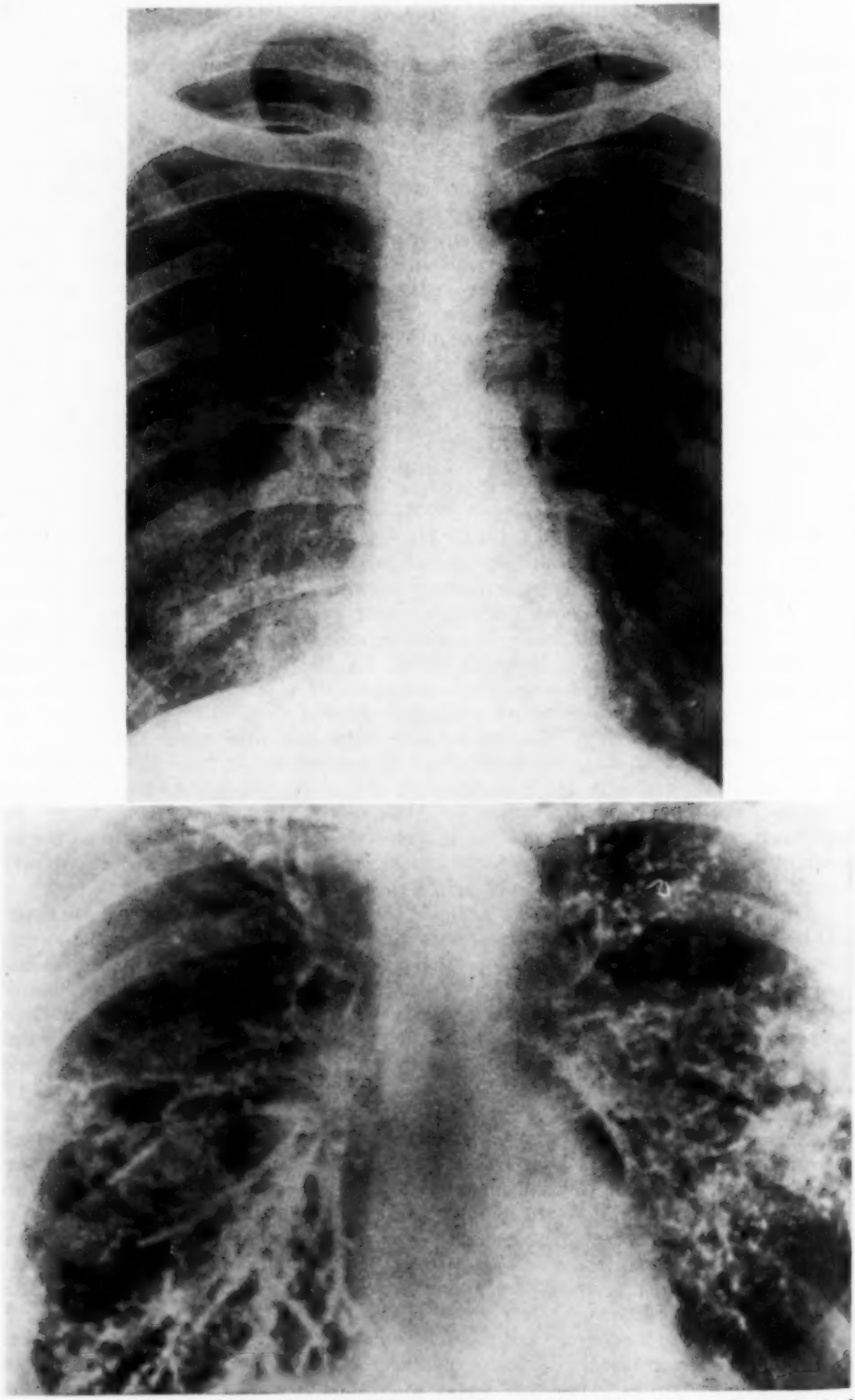

FIG. 3. J. S. B., 41 yr. old white male, worked in mustard 16 months. Complained of cough, easy fatigue, and dyspnea. Roentgenogram shows increased fibrosis at the right lower lobe. Lipiodol studies show minimal bronchiectatic changes in medial segment of right lower lobe.

May 1944, when he had to stop because of severe cough with occasional blood-streaked sputum and general weakness and nervousness. He was hospitalized at a U. S. Marine Hospital in July 1944, at which time physical examination showed many expiratory rhonchi and wheezes together with inconstant moist râles in the right base. There were also a few coarse râles in the left axilla. Sedimentation rate was 13 mm. in one hour. The diagnosis was chronic bronchitis with possible bronchiectasis. He was advised to take postural drainage, ammonium chloride, and to return to light work. Work trial, however, was unsatisfactory and he was returned to compensation status in August 1944, on which he has been ever since. Lipiodol studies done on January 25, 1945, showed no definite evidence of bronchiectasis. His vital capacity was 4800 c.c.

The patient's outstanding symptoms at the present time are weakness on mild exertion and paroxysmal cough precipitated by exertion and change of temperature.

*Case 3.* C. R. B., First Lieutenant, Chemical Warfare Service, age 30. Past history included pneumonia at the age of four with no sequelae. He had scarlet fever at the age of 13. There was no history of any chronic cough. Family history was negative for tuberculosis. He was apparently in good health until February 1943, when he was assigned to a mustard filling plant. He began to have hoarseness and developed complete aphonia several times. His eyes became red, his vision dropped from 20/30 on entrance into the Army to 20/50 in May 1943. At times his vision was so blurred that he could hardly read the headlines in the newspapers. He developed a hacking non-productive cough and had wheezes and chest pain. He remained in the mustard filling plant until June 3, 1943, at which time he was hospitalized for 10 days with a diagnosis of severe, acute, bilateral kerato-conjunctivitis, and moderately acute tracheobronchitis due to mustard. His temperature was 99.4° on admission and dropped to normal after three days. Red blood cells were 4,450,000, hemoglobin 80 per cent; white blood cells 8,150 with 76 per cent neutrophiles, 24 per cent lymphocytes.

After discharge from the hospital he was transferred to the phosphorus manufacturing plant. Following his transfer his vision improved and is now back to normal. His sore throat and hoarseness subsided. From June to September 1943, his sense of taste was definitely impaired but it has gradually returned. He gained about 10 pounds in weight. He continued, however, to have persistent cough precipitated by exertion. It was productive of about two tablespoonfuls of yellowish white sputum. He also had tightness of his chest and dyspnea. In July 1944, he was hospitalized for three weeks with a diagnosis of influenza. Physical examination then showed a few rhonchi in both lungs. The blood count and urinalysis were essentially negative. A roentgenogram showed slightly increased prominence of the bronchovascular markings in the right lower lobe and also in the left mid-lung field, but no definite infiltration. His temperature was 100° on admission and gradually settled down to normal. In August 1944, he was again hospitalized because of cough, chest pain, and temperature of 103°. Physical examination at this time revealed moist râles in the left lower lobe with wheezes and rhonchi throughout the chest. A roentgenogram showed a patchy pneumonitis at the extreme left base. He was treated with sulfadiazine and his temperature dropped to normal after 36 hours. He was discharged after 11 days in the hospital.

Since that time the patient has had intermittent wheezes and chest tightness. He gets dyspneic on moderate exertion. He is very susceptible to upper respiratory infections which tend to "hang on." He gets frequent paroxysmal cough. Roentgen studies on February 16, 1945, showed definite peribronchial thickening at the left base. There was also slightly increased prominence of the bronchovascular markings in the right lower lobe. Vital capacity at this time was 3900 c.c. (87 per cent of normal). Lipiodol studies on April 12, 1943, showed minimal bronchiectasis of the left lower lobe.

*Case 4.* J. L. C., 46 year old white male formerly engaged in farming. He was hired as an assembly operator in the mustard filling plant in December 1942. On January 25, 1943, he was seen in the Out-Patient Department complaining of burning sensations in the eyes, cough, chest pain, and vomiting of blood for two days. Physical examination showed considerable injection of the conjunctival vessels, pharynx was diffusely red, and a few scattered wheezes were audible over both lungs. Temperature was 100°. The diagnosis was bilateral conjunctivitis, pharyngitis, and tracheobronchitis due to mustard gas. He was given five days accident leave. His condition improved and he returned to work. He was treated again in the Out-Patient Department on February 3, 1943, for mustard gas conjunctivitis and tracheobronchitis. On May 22, 1943, he was seen again in the Out-Patient Department at which time his chief complaint was cough. The lungs were clear at this time and the temperature was normal. On June 15, 1943, he again visited the Out-Patient Department. He was complaining of cough, weight loss, and poor appetite. A roentgenogram showed slightly increased prominence of the bronchovascular markings in the lower half of the right lung field. Sputum was negative for tubercle bacilli. On July 13, 1943, he complained of left chest pain in addition to his productive cough. Physical examination showed large rhonchi and musical wheezes over both lungs. Roentgen studies showed definite peribronchial thickening at the left base. The right lung was unchanged since the previous examination. A permanent transfer out of mustard gas was advised at this time.

On March 28, 1944, he was seen again because of cough and tightness in his chest which he claimed was caused by exposure to the colored smoke in which he worked. Physical examination revealed numerous wheezes and rhonchi over both lungs. A roentgenogram showed some clearing in the left base since the previous examination and there was definite peribronchial thickening at the right base. Permanent transfer out of exposure to all types of dust and fumes was advised. On March 7, 1945, he was hospitalized because of persistent cough, wheezing, and chest tightness. Lipiodol studies at this time showed minimal cylindrical bronchiectasis in the left lower lobe. The patient stated that his chest felt much clearer after the lipiodol studies. He was discharged to light duty.

*Case 5.* W. T. W., 24 year old white male, formerly worked in a Civilian Conservation Corps camp and did farming. Past medical history includes mild influenza in 1936, from which he apparently made a complete recovery without any residual cough. He began work in the mustard filling plant on February 8, 1943. His job was to clean up the mustard from the floor after spills or leaks. In April 1943, he developed red eyes, hoarseness, and severe cough. He could not eat or sleep because of his persistent coughing. He was treated in the Out-Patient Department and was given several days sick leave on three occasions when his symptoms became particularly severe.

In February 1944, he was transferred to another department and his symptoms began to improve. His cough and wheezing, however, persisted. He was granted a furlough in June 1944, for induction into the Army but was rejected by the Army doctors (presumably because of his chest findings). He was seen by an allergist who found sensitivity to several proteins but attempted desensitization produced no improvement in the cough. In October 1944, he was seen at the Marine Hospital where physical examination revealed some wheezes and moist râles over both lung fields posteriorly. Sedimentation rate was 7 mm. in one hour. Blood counts were normal. Sputum examination for tubercle bacilli and blood test for syphilis were negative. Lipiodol studies at that time showed no evidence of bronchiectasis. The diagnosis was chronic bronchitis due to poison gas. He was rated as having no disability at that time but was advised to avoid chemical fumes, and to have reëxamination after an interval of four months. In November 1944, he was rehired at the Arsenal. On March 19, 1945, he was again seen in the Out-Patient Department. He still had a

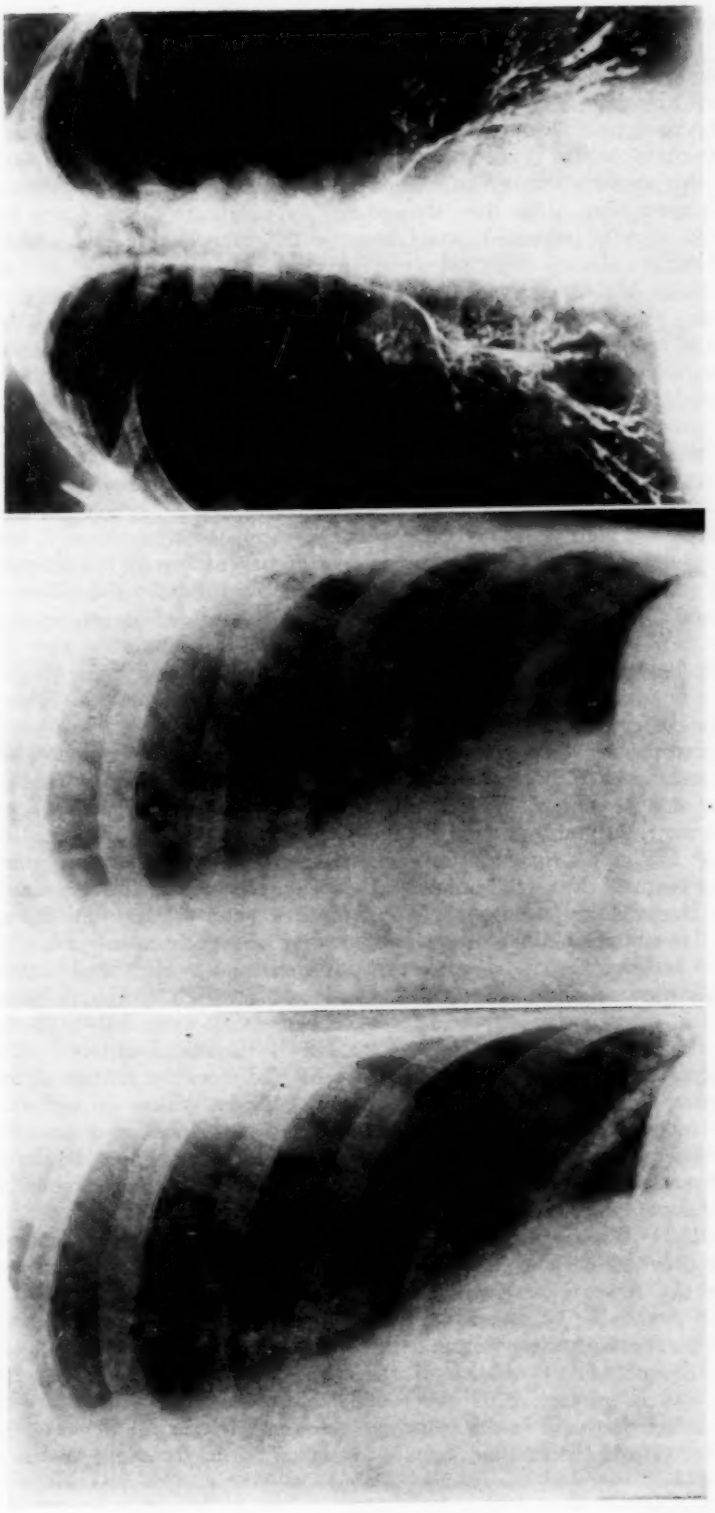

FIG. 4. L. S. M., 28 yr. old white male, worked in mustard 12 months. Has residual cough and foul sputum. December, 6, 1943, definite peribronchial infiltration at left base (? atelectasis). July 10, 1944, considerable resolution of densities noted in previous film. January 3, 1945, lipiodol studies show bronchiectasis left lower lobe.

moderately productive cough, worse on exertion and during change of weather. He stated that he raised about one half teacup of mucoid yellow or white sputum which occasionally had a foul odor in the morning but was never blood streaked. His appetite was fair. He had a wheezing and constant substernal soreness on deep inspiration. Physical examination revealed a few wheezes and rhonchi over the lower half of the left chest audible on deep inspiration. His vital capacity was 5000 c.c.

Although this man had numerous râles and wheezes in both lungs on many examinations, his chest films at no time showed any very definite changes, the findings being limited to slightly increased prominence of the bronchovascular markings in both lower lobes.

*Case 6.* D. G. M., 42 year old white male formerly engaged in farming. Gave no history of any previous chronic lung disease. Began work at the Arsenal in September 1942, and spent 10 months in the mustard filling plant. He had repeated exposure to mustard gas fumes in the winter of 1942, and spring of 1943. He was seen in the Out-Patient Department on numerous occasions and was treated for several mustard burns of the skin as well as mustard vapor conjunctivitis, pharyngitis, and tracheobronchitis. In June 1943, he complained of hoarseness, headache, and severe cough. He had lost 35 pounds in five months. A roentgenogram of the chest showed peribronchial infiltration in the basal portions of both lung fields with obliteration of the costophrenic angle, bilaterally. He was transferred out of mustard filling to another department. Within two months his eyes and throat symptoms subsided but he had a persistent residual cough frequently productive of yellowish white mucopurulent sputum. He also had irregular afternoon fever and dyspnea on slight exertion.

On May 1, 1944, he quit work because of his cough, chest pain, and dyspnea on mild exertion. On June 12, 1944, he developed an extensive pneumonitis of the right mid-lung field. In August 1944, he was seen at a U. S. Marine Hospital where physical examination showed moist râles at both bases. Pulse rate was 90 to 110; sedimentation rate was 26 mm. in one hour. Sputum was negative for tubercle bacilli; blood counts were normal. Roentgenogram at this time showed clearing of the pneumonitis in the right mid-lung field but there was evidence of peribronchial fibrosis in both bases. He was adjudged to be completely disabled temporarily and was advised to take postural drainage, ammonium chloride, and rest. He was seen again at the Marine Hospital on January 31, 1945. He had not worked for the preceding four months. He still complained of cough productive of one cupful of yellow sputum daily. He also had dyspnea and intermittent left chest pain. He stated that he had been taking his postural drainage regularly and had gained about nine pounds in weight. Physical examination showed occasional moist râles over both bases posteriorly. Blood pressure was 112 mm. Hg systolic and 74 diastolic; red blood cells were 4,650,000; hemoglobin 78 per cent; white blood cells 12,550 with a normal differential count; sedimentation rate was 26 mm. in one hour. Lipiodol studies showed extensive bronchiectasis involving the right middle and right lower lobes and also the left lower lobe. The opinion of the chest consultant was that he should be considered disabled for three months and then should be rechecked. In the meantime he was to continue his ammonium chloride and postural drainage.

*Case 7.* R. H. W., 29 year old white male formerly engaged in farming. No history of any previous chronic lung disease. He began work in the mustard filling department on the Arsenal in November 1942. After exposure to mustard fumes for about three months he began to cough and had a burning sensation of the eyes. He worked in the mustard filling department for 11 months and was then transferred to another department. His eyes have returned to normal but his cough has gradually become worse and is productive of about one tablespoonful of thick white phlegm per day. His cough is worse in the morning. He has chest pain and becomes weak and tired easily. He has never had hemoptysis, fever, chills, or night sweats.

He was examined at a Marine Hospital October 26, 1944, at which time his chest was clear. Blood pressure 142 mm. Hg systolic and 96 mm. diastolic; sedimentation rate 5 mm. in one hour; blood test for syphilis negative; red blood cells 5,500,000; hemoglobin 88 per cent; white blood cells 7,150 with a normal differential count. Lipiodol studies showed no evidence of bronchiectasis. Serial roentgenograms of the chest from January 1943, through September 1944, have been practically normal except for minimal accentuation of the bronchovascular markings in the right lower lobe.

*Case 8.* E. P., 28 year old white male. No history of previous chronic lung disease. He was exposed to mustard fumes for eight months, beginning December 1942. After three months he developed sore throat, chest pain, hoarseness, redness of both eyes, and impaired vision. He had to stay away from work on numerous occasions for several days at a time. He was finally transferred to another department. His eye symptoms subsided but his cough persisted. He also had tightness of the chest, wheezing, and undue fatigue on moderate exertion. He was studied at the Marine Hospital in September 1944, where physical examination showed inspiratory and expiratory wheezes over both lungs with coarse moist râles at both bases. Blood pressure was 124 mm. Hg systolic and 86 mm. diastolic; pulse 76; blood counts normal; sedimentation rate 3 mm. in one hour. Repeated sputum examinations were negative for tubercle bacilli. A roentgenogram showed increased prominence of the bronchovascular markings in both lower lobes and lipiodol studies showed minimal bronchiectasis in the right lower lobe. He was rated as 25 per cent disabled and was placed on postural drainage and ammonium chloride therapy.

He was reëxamined at Marine Hospital in November 1944, and stated that he had gained seven pounds but he still coughed in the morning and raised about a teaspoonful of white phlegm. Physical examination of the chest at that time was essentially negative and the opinion was that he could return to light work, that he should have no disability and that he was to be rechecked in six months. Postural drainage and ammonium chloride were to be continued. He was admitted again to the Station Hospital for five days in December 1944, because of an acute bronchitis superimposed on his chronic bronchitis. His temperature at that time was 99.2°, and loud rhonchi could be heard throughout both lungs. He was discharged on December 23, 1944. He was examined at weekly intervals in January 1945, at which time numerous rhonchi and wheezes could be heard in both lungs. His vital capacity was 4600 c.c. He was tried on a light job but had to stop at the end of five days because of persistent cough. He was then given a 30 day medical furlough. He returned to a light job on March 9, 1945. At present his residual symptoms consist of wheezing and paroxysmal cough on exertion. His appetite is good.

*Case 9.* J. L. B., 29 year old white female. She had malaria at the age of 18 but has no history of any previous lung disease. From January to June 1943, she worked in the mustard filling plant as a supervisor. She had to be around small spills quite often and could not wear her mask at times. She was treated in the Out-Patient Department several times for mustard tracheobronchitis, and conjunctivitis. Following transfer out of the mustard filling plant her cough became less but still persists. It is productive of about one fourth cupful of white mucoid sputum. Cough is worse at night. Fumes and smoke will often precipitate a coughing spell. She has occasional wheezing but no dyspnea and she states that she can do a day's work fairly well. Her vital capacity is 3700 c.c. Physical examination reveals a few moist râles at the extreme right base. Roentgenogram of the chest in July 1943, showed slightly increased prominence of the bronchovascular markings, right lower lobe. Follow-up roentgenogram on March 29, 1945, showed no essential change in the findings. Lipiodol studies have not been done.

*Case 10.* W. R. S., 30 year old white male formerly engaged in farming. Past history is negative except for influenza at the age of 26. Apparently this cleared

without residual damage. He worked in mustard for about seven months beginning November 1942. He developed symptoms of mustard vapor conjunctivitis three weeks after he was hired. He was seen on numerous occasions in the Out-Patient Department from November 1942, to June 1943, primarily for conjunctivitis and severe tracheobronchitis. He expectorated blood on several occasions.

He was not seen again at the hospital until March 29, 1945, at which time he complained of cough productive of about one-half cupful of yellow mucoid sputum which was occasionally foul but not blood streaked. He had undue dyspnea on exertion, chest tightness, and wheezing. Cough was worse at night on lying down and he often was unable to sleep until he could get rid of his mucus. He had frequent paroxysms of cough when he became overheated. He also stated that he was very nervous and had frequent afternoon temperature elevation. His appetite was fair; his weight was stationary. Physical examination at that time showed numerous wheezes and rhonchi throughout both lungs, more marked on the right side with many moist râles at the right base. Vital capacity was 2800 c.c. Roentgen studies of the chest showed increased bronchovascular markings in the right lower lobe. Lipiodol studies revealed minimal bronchiectasis in the medial branches of the right lower lobe bronchus.

## Discussion

Mustard vapor, like other irritant gases, produces an inflammatory reaction in the mucosa of the respiratory tract. The severity of the inflammatory process will vary with the concentration of the gas, the length of exposure, and the susceptibility of the individual. But, although the inflammation is most severe in the upper respiratory tract, decreasing in intensity downward, it is the smaller bronchi and bronchioles which tend to develop residual pathologic changes due to the accumulation of secondarily infected secretions and necrotic tissues. "The peribronchial thickening" often noted in the basal portions of the lung fields on roentgenograms may well represent small areas of patchy atelectasis. The stage is then set for the development of bronchiectasis.

Fifty-five out of 85 patients on whom lipiodol studies have been done here and at the Marine Hospital, Memphis, showed definite evidence of bronchiectasis ranging from minimal involvement of a few bronchi in one lower lobe to extensive involvement of as many as four lobes.

It must be emphasized at this point that, although the roentgenogram is of extreme importance in the study of most chest diseases, its value is definitely limited in chronic mustard gas bronchitis. A patient may have negative bronchograms and an apparently normal chest film and yet he may be partially disabled because of a persistent paroxysmal cough. Roentgen studies can show us structural changes when they exceed a certain degree but they cannot demonstrate disturbed physiology of the bronchial musculature and mucosa.

Physical findings in a patient with chronic mustard bronchitis are usually confined to the chest which shows scattered wheezes and rhonchi with occasional moist râles at one or both bases on deep inspiration or after coughing. However, even a well established case of bronchitis may occasionally sound normal on auscultation. The physician should not be misled by the

scarcity of the chest findings on a single examination. Such factors as the dampness of the weather, the type of medication used, and the thoroughness of the preceding postural drainage will influence the amount of secretions in the bronchial tree which in turn largely determine the presence or absence of adventitious sounds in the lungs.

The vital capacity of the chronic mustard bronchitis case is usually diminished. However, even this is not a completely reliable index of a man's disability. One of our patients had a vital capacity of 4800 c.c. (102 per cent of normal for a man of his size), yet he could not hold down any job because moderate exertion would usually precipitate a severe coughing spell which left him in a cold sweat, weak, and trembling.

Our present routine treatment of chronic mustard bronchitis consists of postural drainage, high fluid intake, 60 grains of ammonium chloride daily, and removal of the patient from all contact with smoke, fumes, or dust. Steam inhalations are often of value in easing the tight sensation and wheezing in the chest. An occasional dose of codeine may be indicated for relief of a harassing non-productive cough that is exhausting the patient, but its prolonged use is harmful since it inhibits drainage of the bronchial secretions.

Most patients feel considerable relief of wheezing and chest tightness for several days or weeks after a lipiodol instillation. In fact many of them refer to it as the "oil treatment."

Barach et al.[5] in New York, and Olsen [6] at the Mayo Clinic, have recently reported good results with the use of nebulized penicillin (penicillin aerosol) in cases of chronic bronchitis and bronchiectasis. Arrangements are being made for a therapeutic trial of penicillin nebulin on some of our patients.

On theoretical grounds the removal of patients to a dryer climate should be helpful.

## Summary

1. Many persons employed in the handling of mustard gas and exposed to small quantities of the vapor over a long period of time will develop a residual chronic bronchitis which may go on to bronchiectasis.

2. Many of these patients are partially or totally disabled because of a persistent paroxysmal cough on moderate exertion.

3. History and clinical findings are most important in the diagnosis of chronic mustard bronchitis. Roentgen studies may be of little value unless definite bronchiectasis can be demonstrated on lipiodol studies.

4. Treatment consists of postural drainage, high fluid intake, and 60 grains of ammonium chloride daily. Patients should be removed from any contact with smoke, fumes, or dust. Nebulized penicillin is under therapeutic trial at the present time.

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# COMPARISON OF THE CLINICAL USE OF PROTAMINE ZINC INSULIN AND GLOBIN INSULIN IN EQUAL DOSES*

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It is generally thought now that the use of a long-acting insulin alone or mixed with unmodified insulin is preferable to the use of unmodified insulin alone in the control of patients who require insulin in addition to a measured diet. At the present time, however, there is confusion regarding the best preparation or combination of insulins for routine use. Inasmuch as most diabetics are treated by general practitioners or internists who do not specialize in the treatment of diabetic patients it is important that the treatment of diabetic patients should not become too complicated and should still be adequate. We have become interested in this problem and for about two years have undertaken an investigation of the relative merits of the use of globin insulin and protamine zinc insulin in equal doses. Recently we have been selecting the relatively few patients for treatment with combinations of protamine zinc insulin and unmodified insulin who have not been adequately controlled on either globin insulin or protamine zinc insulin. The present report is concerned only with our investigation of the relative merits of the use of protamine zinc insulin and globin insulin with zinc.

As a basis for the investigation we have assumed that diabetic patients are not well controlled unless their measured diet is close to normal in composition when sugar is omitted, unless they rarely excrete more than five grams of dextrose in the urine each day, and unless their blood sugar is not over 175 mg. per cent when it is determined before each meal, one hour after each meal and at 11:00 p.m. We have made these seven blood sugar determinations on each of two and usually more days in each case as a part of this study, but we are not advocating this number of blood sugar determinations in a day for routine use. Moderately good or adequate control, especially in older arteriosclerotic persons, probably exists if the insulin given prevents blood sugar levels higher than 200 mg. per cent and if hypoglycemia is prevented.

Our patients have all been hospitalized at the Gallinger Municipal Hospital, a teaching institution of 1,650 beds in which because of limitations of the diet kitchen we have considered it best to limit our diet to three basic

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From the Diabetic Service of the Gallinger Municipal Hospital, and the Georgetown University and George Washington University Schools of Medicine, Departments of Medicine.

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formulae, bringing the number of calories when necessary to a larger figure by the addition of butter or a meat sandwich with milk. The formulae of these three diets are as follows:

No. 1: C180, P60, F60 (3 meals with one third of the total glucose value per meal).

No. 2: C225, P70, F70 (3 meals with one third of the total glucose value per meal).

No. 3: C225, P70, F77 (3 meals with one fifth of the total glucose value at breakfast, two fifths at the noon meal, and two fifths at the evening meal).

After the patient is out of acidosis, if he entered the hospital in that state, or after he has become stabilized as well as possible in regard to any complication that may have existed or continues to exist, he is given the diet that he is to remain on for the duration of the investigation. This is No. 3 above, unless rare and special conditions lead to the use of one of the other diets. Later, in some cases, according to a considered need, a bedtime feeding of a meat sandwich and a glass of milk is added, usually when protamine zinc insulin is being used, or in a few cases a midafternoon feeding of similar content for patients receiving globin insulin.

In many cases when the patient's condition allows it on admission or soon afterwards his blood sugar curve is determined before insulin is given or after withdrawal of insulin for a day. This curve is made by determining the concentration of dextrose in samples of venous blood drawn at 7:00 a.m., 9:00 a.m., 11:00 a.m., 1:00 p.m., 4:00 p.m., 7:00 p.m., and 11:00 p.m. The analyses are made by a fulltime skilled technician or medical resident assigned to this work. The urine is collected for the 24 hours daily or as often as is needed to determine how much dextrose is being excreted on a given dose of insulin.

Insulin, either protamine zinc or globin, is then given each morning at 7:00 in an arbitrary amount and rapidly changed until the optimum amount is being used, rarely over 80 units, the state of the diabetes being ascertained by means of the amount of dextrose excreted in the urine in 24 hours and by blood sugar determinations made one hour after breakfast. When the amount of dextrose in the 24-hour urine becomes 5 grams or less and the blood sugar one hour after breakfast is 175 mg. per cent or less, if possible a blood sugar curve is made. The insulin is then rapidly changed to the other form and the procedure repeated. At least three days and usually a week has been allowed on each dose and form of insulin before making blood sugar curves. About half of the patients were treated first with each form of insulin and then changed to the other preparation.

## Material

Of all the diabetic patients hospitalized during the period of this study 84 were treated for comparative purposes on both globin and protamine

zinc insulins with blood sugar curves obtained while they were being given an equal dose of each form of insulin. Some of these patients were similarly studied on other admissions with a total of 97 hospital admission case studies, providing 587 pairs of blood sugar values comparing globin insulin with protamine zinc insulin.

Careful scrutiny of each case has been used to be quite certain that changes in diet, exercise, infection, healing fractures, hepatic disease or other evident factors did not distort the comparison.

## Results

A comparison of the blood sugar curves of these 97 case studies on both forms of insulin in equal doses gave the following results:

I. Number of patients controlled better by globin insulin than by protamine zinc insulin ..... 70

1. Adequately (no blood sugars over 200) ..... 50
2. Inadequately (at least one blood sugar over 200) ..... 20

II. Number of patients better controlled by protamine zinc insulin than by globin insulin ..... 22

1. Adequately (no blood sugar over 200) ..... 19
2. Inadequately (at least one blood sugar over 200) ..... 3

III. Number of patients well controlled by both forms, no blood sugar levels being over 175 mg. per cent ..... 14

IV. Number of patients moderately well controlled by both forms, meaning that some blood sugar levels were between 175 mg. per cent and 200 mg. per cent ..... 7

V. Number of patients not adequately controlled by either form of insulin, some blood sugar levels being 200 mg. per cent or more ..... 24

These figures indicate definitely that for these 84 hospitalized patients with 97 comparisons of blood sugar values, using the same diet and the same number of units of each form of insulin, globin insulin was superior in bringing about control as judged by these rigid chemical criteria. On the other hand, there was a fair number of patients "inadequately controlled" by globin insulin on the regimen used at the time of the comparative curves; this does not mean, however, that these patients were incapable of being controlled adequately for ordinary clinical purposes on some other dosage or combination of insulins.

When these patients were compared with attention to all factors (blood sugar curve, hypoglycemia, and general state), 65 were controlled better with globin insulin, 25 with protamine zinc insulin, and seven equally well with the two forms in equal doses. This type of analysis is important in addition to that above, since a smoother blood sugar curve, avoidance of low blood sugar levels, and sense of well-being are desirable.

A comparison is made in table 1 of the blood sugar curves and 24-hour

TABLE I

Comparison of blood sugar curves and 24 hour urine sugar in patients receiving equal doses of globin zinc insulin and protamine zinc insulin, and no insulin

For each patient: a. Top Line—curve with globin zinc insulin (G)
b. Middle Line—curve with protamine zinc insulin (P)
c. Bottom Line—curve with no insulin (0)

| Patient | Age | Units, Dose | Date | Blood Sugar Curve | | | | | | | Gm. Sugar 24 Hours' Urine |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 7:00 a.m. | 9:00 a.m. | 11:00 a.m. | 1:00 p.m. | 4:00 p.m. | 7:00 p.m. | 11:00 p.m. | |
| 1 | 60 | 55-G | 3/28/45 | 148 | 163 | 182 | 154 | 125 | 163 | 174 | 0 |
| | | 55-P | 3/23/45 | 103 | 211 | 151 | 211 | 238 | 297 | 186 | 0 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 1 | 60 | 50-G | 7/ 3/45 | 118 | 174 | — | 186 | 87 | 85 | 89 | 0 |
| | | 50-P | 7/11/45 | 93 | 167 | — | 108 | 129 | 129 | 125 | 27 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 2 | 53 | 20-G | 4/20/45 | 53 | 143 | 157 | 89 | 78 | 83 | 95 | 0 |
| | | 20-P | 4/10/45 | 81 | 121 | 114 | 140 | 138 | 190 | 167 | 0 |
| | | 0 | 3/ 9/45 | 250 | 222 | 258 | 297 | 258 | 364 | 320 | — |
| 3 | 43 | 80-G | 6/10/45 | 174 | — | — | 276 | — | — | — | 21 |
| | | 80-P | 6/ 7/45 | 267 | — | — | 444 | — | — | — | 42 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 4 | 52 | 45-G | 11/22/45 | 143 | — | 138 | 154 | — | — | — | — |
| | | 45-P | 11/11/45 | 116 | — | 182 | 138 | — | — | — | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 5 | 34 | 25-G | 11/20/44 | — | 96 | 82 | 102 | 103 | 209 | 209 | 0 |
| | | 25-P | 11/13/44 | — | 242 | 187 | 189 | 217 | 202 | 131 | 4.2 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 6 | 46 | 75-G | 5/11/45 | 67 | 143 | 60 | 108 | — | — | — | 0 |
| | | 75-P | 5/ 7/45 | 80 | 205 | 125 | 138 | — | — | — | 0 |
| | | 0 | 4/13/45 | 267 | 364 | 382 | 432 | 364 | 422 | 304 | 11.3 |
| 7 | 46 | 40-G | 5/ 1/45 | 161 | 250 | 167 | 228 | 200 | 250 | 276 | 9.9 |
| | | 40-P | 4/24/45 | 77 | 95 | 69 | 95 | 174 | 235 | 138 | 6.3 |
| | | 0 | 4/ 9/45 | 211 | 333 | 100 | 333 | 216 | 216 | 222 | 30 |

TABLE I—*Continued*

| Patient | Age | Units, Dose | Date | Blood Sugar Curve | | | | | | | Gm. Sugar 24 Hours' Urine |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 7:00 a.m. | 9:00 a.m. | 11:00 a.m. | 1:00 p.m. | 4:00 p.m. | 7:00 p.m. | 11:00 p.m. | |
| 8 | 52 | 15-G | 5/28/45 | 174 | 129 | 129 | 242 | 77 | 182 | 108 | 0 |
| | | 15-P | 6/ 1/45 | 118 | 216 | 133 | 167 | 81 | 182 | 105 | 0 |
| | | 0 | 5/17/45 | 235 | 308 | 182 | 235 | 143 | 222 | 174 | 0 |
| 9 | 80 | 30-G | 9/28/45 | 95 | 105 | 83 | 118 | 133 | — | — | 0 |
| | | 30-P | 11/ 8/45 | 83 | 129 | 118 | 161 | 143 | — | — | 0 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 10 | 50 | 40-G | 7/ 2/45 | 87 | 143 | 160 | 200 | 160 | 105 | 180 | — |
| | | 40-P | 6/26/45 | 62 | 121 | 129 | 108 | 91 | 154 | 91 | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 11 | 64 | 20-G | 4/26/45 | 72 | 211 | 103 | 161 | 87 | 125 | 103 | — |
| | | 20-P | 4/17/45 | 100 | 138 | 129 | 121 | 80 | 100 | 111 | — |
| | | 0 | 11/27/45 | 118 | 111 | 133 | 205 | 211 | 326 | 325 | 5 |
| 12 | 63 | 10-G | 3/13/45 | 133 | 200 | 235 | — | 143 | 211 | 174 | 0 |
| | | 10-P | 3/ 5/45 | 182 | 235 | 242 | — | 151 | 202 | 135 | 0 |
| | | 0 | 2/17/45 | 195 | 286 | 186 | 276 | 178 | 364 | 170 | — |
| 13 | 39 | 30-G | 7/ 6/45 | 125 | — | 114 | 138 | 182 | — | 71 | 0 |
| | | 30-P | 7/11/45 | 77 | — | 154 | 154 | 133 | — | 143 | 0 |
| | | 0 | 6/18/45 | 308 | 320 | 250 | 320 | 267 | 250 | 228 | 30 |
| 14 | 52 | 60-G | 7/31/45 | 52 | — | 74 | 154 | 91 | 143 | 56 | 0 |
| | | 60-P | 8/ 3/45 | 83 | — | 121 | 200 | 170 | 205 | 161 | 0 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 15 | 57 | 25-G | 7/24/45 | 103 | 160 | 149 | 174 | 138 | 143 | 103 | 0 |
| | | 25-P | 7/19/45 | 97 | 167 | 129 | 216 | 95 | 143 | 129 | 0 |
| | | 0 | 12/21/44 | 125 | — | 286 | 297 | 250 | 220 | 160 | 0 |
| 16 | 73 | 15-G | 7/11/45 | 91 | 138 | 62 | 167 | 154 | 71 | 67 | — |
| | | 15-P | 7/ 3/45 | 91 | 134 | 111 | 122 | 83 | 78 | 89 | — |
| | | 0 | 5/23/45 | 190 | 211 | 267 | 320 | 286 | 320 | 216 | 15 |

TABLE I—*Continued*

| Patient | Age | Units, Dose | Date | Blood Sugar Curve | | | | | | | Gm. Sugar 24 Hours' Urine |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 7:00 a.m. | 9:00 a.m. | 11:00 a.m. | 1:00 p.m. | 4:00 p.m. | 7:00 p.m. | 11:00 p.m. | |
| 17 | 59 | 35-G | 3/26/45 | 145 | — | 154 | 222 | — | 228 | — | 0 |
| | | 35-P | 3/20/45 | 149 | — | 128 | 182 | — | 190 | — | 0 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 18 | 60 | 45-G | 4/26/45 | 67 | 200 | 100 | 73 | 64 | 85 | 77 | 0 |
| | | 45-P | 5/17/45 | 134 | 151 | 160 | 160 | 105 | 157 | 154 | 0 |
| | | 0 | 3/24/45 | 444 | 445 | — | 333 | 362 | 340 | 280 | 1.3 |
| 18 | 60 | 30-G | 6/29/45 | 87 | 170 | 93 | — | 87 | — | — | — |
| | | 30-P | 6/21/45 | 125 | 190 | 148 | — | 105 | — | — | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 19 | 44 | 25-G | 10/ 4/44 | 145 | 235 | 160 | 235 | 129 | 190 | 267 | — |
| | | 25-P | 11/ 2/44 | 125 | 242 | 242 | 153 | 161 | 218 | 135 | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 20 | 70 | 30-G | 7/30/45 | 77 | 138 | 108 | 140 | 129 | 182 | 154 | 2.6 |
| | | 30-P | 8/ 3/45 | 81 | 161 | 133 | 154 | 149 | 174 | 143 | 1.1 |
| | | 0 | 7/23/45 | — | — | — | — | — | — | 333 | — |
| 21 | 25 | 80-G | 7/ 5/45 | 71 | 167 | 111 | 174 | 108 | 211 | 154 | 1.6 |
| | | 80-P | 7/13/45 | 191 | 286 | 333 | 500 | 364 | 333 | 222 | 19 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 22 | 52 | 20-G | 4/24/45 | 53 | — | 97 | 111 | — | 120 | 133 | 0 |
| | | 20-P | 4/ 2/45 | 81 | — | 121 | 133 | — | 133 | 111 | 0 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 23 | 65 | 20-G | 10/27/45 | 100 | 118 | 95 | — | 74 | 118 | — | — |
| | | 20-P | 10/15/45 | 133 | 143 | 154 | — | 151 | 143 | — | — |
| | | 0 | 9/26/45 | 157 | 211 | 450 | 250 | — | — | — | 17.5 |
| 24 | 56 | 50-G | 3/29/45 | 118 | 222 | 133 | 216 | 95 | 173 | 75 | 0 |
| | | 50-P | 3/23/45 | 143 | 228 | 186 | 170 | 158 | 242 | 147 | 0 |
| | | 0 | — | — | — | — | — | — | — | — | — |

TABLE I—*Continued*

| Patient | Age | Units, Dose | Date | Blood Sugar Curve | | | | | | | Gm. Sugar 24 Hours' Urine |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 7:00 a.m. | 9:00 a.m. | 11:00 a.m. | 1:00 p.m. | 4:00 p.m. | 7:00 p.m. | 11:00 p.m. | |
| 25 | 68 | 60-G | 8/17/45 | — | — | 133 | 170 | 143 | — | 135 | 0 |
| | | 60-P | 8/23/45 | — | — | 118 | 148 | 138 | — | 95 | 0 |
| | | 0 | 8/ 4/45 | 186 | 286 | — | — | — | 308 | 258 | 28 |
| 26 | 36 | 80-G | 3/ 6/45 | 154 | 205 | 286 | 308 | 125 | 133 | 52 | 0 |
| | | 80-P | 2/28/45 | 40 | 121 | 143 | 267 | 205 | 382 | 235 | 20 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 27 | 58 | 30-G | 7/23/45 | 100 | 128 | — | 160 | 125 | 133 | 161 | 3.7 |
| | | 30-P | 7/30/45 | 133 | 222 | — | 134 | 125 | 200 | 105 | 4.8 |
| | | 0 | 7/17/45 | — | — | — | — | — | — | 444 | — |
| 28 | 70 | 20-G | 4/ 2/45 | 163 | 174 | — | — | 182 | 167 | — | 0 |
| | | 20-P | 4/ 9/45 | 174 | 250 | — | — | 174 | 170 | — | 0 |
| | | 0 | 3/16/45 | 211 | 163 | 222 | 195 | 205 | 222 | 175 | 0 |
| 28 | 70 | 30-G | 4/26/45 | 83 | 105 | 70 | 114 | 91 | 103 | 95 | — |
| | | 30-P | 4/16/45 | 71 | 108 | 143 | 121 | 111 | 133 | 108 | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 29 | 70 | 25-G | 5/ 1/45 | 174 | 85 | 87 | 70 | 60 | 151 | 75 | 0 |
| | | 25-P | 5/16/45 | 70 | 95 | 103 | 211 | 258 | 267 | 163 | 2.0 |
| | | 0 | 4/ 6/45 | 333 | — | — | — | 286 | 308 | — | — |
| 30 | 53 | 75-G | 11/28/44 | 70 | 67 | 105 | 128 | — | 110 | 94 | 0 |
| | | 75-P | 11/21/44 | 43 | 108 | 86 | 348 | — | 198 | 89 | 33.9 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 31 | 43 | 30-G | 3/26/45 | 75 | 149 | 154 | 167 | 108 | 163 | 138 | 0 |
| | | 30-P | 3/19/45 | 74 | 151 | 205 | 200 | 85 | 182 | 151 | 0 |
| | | 0 | 9/20/44 | 187 | 235 | — | — | — | — | — | — |
| 32 | 60 | 30-G | 4/24/45 | 138 | 149 | — | 200 | 105 | 114 | — | 0 |
| | | 30-P | 5/ 2/45 | 77 | 190 | — | 222 | 163 | 235 | — | 9 |
| | | 0 | 4/ 7/45 | 182 | 195 | 160 | 195 | 78 | 211 | 149 | — |

TABLE I--*Continued*

| Patient | Age | Units, Dose | Date | Blood Sugar Curve | | | | | | | Gm. Sugar 24 Hours' Urine |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 7:00 a.m. | 9:00 a.m. | 11:00 a.m. | 1:00 p.m. | 4:00 p.m. | 7:00 p.m. | 11:00 p.m. | |
| 33 | 56 | 65-G | 5/ 2/45 | — | 182 | 114 | 258 | 150 | 182 | 211 | 0 |
| | | 65-P | 5/25/45 | — | 108 | 170 | 138 | 62 | 170 | 182 | 0 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 33 | 56 | 55-G | 4/23/45 | 138 | — | — | — | 200 | 286 | — | 5.9 |
| | | 55-P | 4/18/45 | 143 | — | — | — | 200 | 276 | — | 6.7 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 34 | 42 | 50-G | 8/13/45 | 87 | — | 77 | — | 97 | 133 | — | 12 |
| | | 50-P | 8/21/45 | 89 | — | 118 | — | 211 | 191 | — | 10 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 35 | 52 | 40-G | 11/16/44 | 59 | 275 | 225 | 270 | 218 | 247 | 223 | 11.7 |
| | | 40-P | 10/31/44 | 57 | 83 | 229 | 317 | 303 | 412 | 84 | 22.8 |
| | | 0 | 10/17/44 | 267 | — | — | — | — | — | — | 54 |
| 36 | 60 | 20-G | 3/14/45 | 85 | — | 120 | 100 | — | 91 | 83 | 0 |
| | | 20-P | 3/ 5/45 | 125 | — | 122 | 143 | — | 70 | 68 | 0 |
| | | 0 | 2/19/45 | 286 | — | — | — | — | — | — | 22 |
| 37 | 53 | 25-G | 10/31/44 | 136 | 195 | 190 | 160 | 77 | 186 | 207 | 0 |
| | | 25-P | 11/13/44 | 93 | 85 | 86 | 133 | 93 | 94 | 51 | 0 |
| | | 0 | 9/13/44 | 235 | 195 | — | — | — | — | — | 21.4 |
| 38 | 56 | 30-G | 3/ 7/45 | 154 | 186 | — | 190 | 104 | 218 | 178 | 0 |
| | | 30-P | 2/23/45 | 100 | 211 | — | 222 | 163 | 235 | 200 | 0 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 38 | 56 | 40-G | 5/28/45 | 138 | 190 | 67 | 121 | 63 | 114 | 148 | — |
| | | 40-P | 5/ 8/45 | 133 | 195 | 148 | 195 | 178 | 145 | 149 | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 39 | 52 | 20-G | 5/18/45 | 105 | — | 103 | 178 | — | — | — | 0 |
| | | 20-P | 5/ 8/45 | 114 | — | 125 | 167 | — | — | — | 1.2 |
| | | 0 | 4/19/45 | 250 | — | — | — | — | — | — | — |

TABLE I—*Continued*

| Patient | Age | Units, Dose | Date | Blood Sugar Curve | | | | | | | Gm. Sugar 24 Hours' Urine |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 7:00 a.m. | 9:00 a.m. | 11:00 a.m. | 1:00 p.m. | 4:00 p.m. | 7:00 p.m. | 11:00 p.m. | |
| 40 | 59 | 30-G | 1/ 9/45 | 143 | — | 143 | 183 | 100 | 174 | 128 | 0 |
| | | 30-P | 2/ 1/45 | 97 | — | 174 | 167 | 191 | 228 | 143 | 0 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 40 | 59 | 40-G | 4/ 3/45 | 129 | 138 | 100 | 111 | 129 | — | 114 | — |
| | | 40-P | 3/16/45 | 87 | 167 | 174 | 167 | 105 | — | 74 | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 40 | 59 | 30-G | 6/ 4/45 | 83 | 163 | 91 | 178 | 80 | 129 | 118 | — |
| | | 30-P | 5/16/45 | 89 | 182 | 167 | 186 | 114 | 143 | 70 | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 40 | 59 | 25-G | 7/ 3/45 | 108 | 160 | 148 | 235 | 124 | — | 114 | — |
| | | 25-P | 6/24/45 | 95 | 195 | 205 | 129 | 182 | — | 193 | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 41 | 48 | 10-G | 7/ 7/45 | 129 | — | 129 | 138 | 129 | 95 | 89 | 0 |
| | | 10-P | 7/13/45 | 87 | — | 118 | 143 | 87 | 200 | 103 | 0 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 42 | 29 | 50-G | 3/19/45 | 67 | 170 | — | 174 | 136 | 195 | 132 | 0 |
| | | 50-P | 3/14/45 | 83 | 170 | — | 134 | 108 | 167 | 74 | 0 |
| | | 0 | 2/23/45 | 211 | 222 | — | 297 | 276 | 400 | 308 | 41 |
| 43 | 52 | 15-G | 7/ 7/45 | 91 | 108 | 161 | 133 | 114 | — | 133 | 0 |
| | | 15-P | 7/13/45 | 87 | 267 | 190 | 167 | 100 | — | 200 | 2 |
| | | 0 | 6/ 8/45 | — | — | 333 | 348 | — | — | — | — |
| 44 | 36 | 25-G | 12/18/44 | 148 | 222 | 105 | 186 | 125 | — | 167 | 1.2 |
| | | 25-P | 11/28/44 | 125 | 190 | 151 | 168 | 138 | — | 171 | 3.4 |
| | | 0 | 11/16/44 | 173 | 229 | 179 | 245 | 186 | 245 | 259 | 11.2 |
| 45 | 46 | 50-G | 7/11/45 | 100 | 89 | 157 | 163 | 143 | 250 | 200 | 1.3 |
| | | 50-P | 7/ 7/45 | 148 | 87 | 170 | 174 | 182 | 200 | 91 | 3.0 |
| | | 0 | 6/25/45 | — | — | — | — | 364 | — | — | — |

TABLE I—*Continued*

| Patient | Age | Units, Dose | Date | Blood Sugar Curve | | | | | | | Gm. Sugar 24 Hours' Urine |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 7:00 a.m. | 9:00 a.m. | 11:00 a.m. | 1:00 p.m. | 4:00 p.m. | 7:00 p.m. | 11:00 p.m. | |
| 46 | 56 | 35-G | 11/ 7/45 | 83 | 83 | 129 | — | 250 | — | — | — |
| | | 35-P | 10/30/45 | 103 | 200 | 167 | — | 200 | — | — | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 47 | 49 | 75-G | 8/ 2/45 | 100 | — | 114 | 125 | 77 | 174 | 167 | 0 |
| | | 75-P | 8/13/45 | 81 | — | 77 | 111 | 95 | 170 | 81 | 0 |
| | | 0 | 7/ 7/45 | — | 364 | — | — | — | — | — | — |
| 48 | 46 | 25-G | 7/16/45 | 71 | 129 | 111 | 167 | 114 | 149 | 111 | 3.8 |
| | | 25-P | 7/23/45 | 157 | 205 | 174 | 174 | 182 | 205 | 200 | 8.5 |
| | | 0 | 7/11/45 | 200 | — | — | 258 | 286 | 250 | 258 | 19.2 |
| 49 | 40 | 25-G | 11/20/45 | 118 | — | 149 | 133 | 186 | 182 | — | — |
| | | 25-P | 11/11/45 | 95 | — | 105 | 178 | 128 | 190 | — | — |
| | | 0 | 11/ 5/45 | 235 | — | — | — | — | — | — | — |
| 50 | 73 | 50-G | 4/ 9/45 | 100 | 182 | 144 | 149 | 54 | — | 121 | 0 |
| | | 50-P | 4/17/45 | 121 | 216 | 170 | 157 | 174 | — | 118 | 0 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 51 | 33 | 20-G | 7/26/45 | 143 | 216 | 114 | 211 | 105 | 161 | 157 | 3.3 |
| | | 20-P | 7/31/45 | 121 | 205 | 200 | 222 | 174 | 174 | 167 | 6.0 |
| | | 0 | 7/ 1/45 | 242 | — | 267 | 333 | 228 | 242 | 211 | 19.5 |
| 52 | 63 | 30-G | 3/27/45 | 133 | 160 | 125 | 211 | 151 | 167 | 161 | — |
| | | 30-P | 3/19/45 | 121 | 126 | 100 | 133 | 100 | 136 | 85 | — |
| | | 0 | 3/ 7/45 | 200 | 250 | 297 | 308 | 222 | 320 | 221 | 3.2 |
| 52 | 63 | 35-G | 4/23/45 | 125 | 138 | 69 | 93 | 53 | 118 | 174 | — |
| | | 35-P | 4/12/45 | 129 | 151 | 108 | 182 | 114 | 149 | 118 | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 52 | 63 | 20-G | 7/ 5/45 | 103 | — | 182 | 125 | 120 | 105 | — | — |
| | | 20-P | 6/21/45 | 105 | — | 62 | 157 | 114 | 100 | — | — |
| | | 0 | — | — | — | — | — | — | — | — | — |

TABLE I—*Continued*

| Patient | Age | Units, Dose | Date | Blood Sugar Curve | | | | | | | Gm. Sugar 24 Hours' Urine |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 7:00 a.m. | 9:00 a.m. | 11:00 a.m. | 1:00 p.m. | 4:00 p.m. | 7:00 p.m. | 11:00 p.m. | |
| 53 | 50 | 30-G | 10/ 2/45 | 133 | 138 | — | 129 | 228 | 200 | 242 | 30 |
| | | 30-P | 10/ 8/45 | 190 | 267 | — | 235 | 222 | 297 | 211 | 43 |
| | | 0 | 9/27/45 | 333 | 308 | 125 | 348 | 242 | 336 | 308 | 88 |
| 54 | 42 | 50-G | 7/ 7/45 | 62 | 108 | 118 | 138 | 75 | 167 | 103 | 0 |
| | | 50-P | 7/12/45 | 167 | 200 | 161 | 228 | 167 | 154 | 95 | 9.4 |
| | | 0 | 5/23/45 | 308 | 286 | 242 | 348 | 250 | 333 | 348 | 40 |
| 55 | 60 | 40-G | 3/12/45 | 129 | 250 | 211 | 182 | 138 | 170 | — | 0 |
| | | 40-P | 3/ 5/45 | 114 | 190 | 178 | 170 | 121 | 178 | — | 0 |
| | | 0 | — | — | — | — | — | — | — | — | 19 |
| 56 | 52 | 15-G | 7/10/45 | 85 | 83 | 163 | 163 | 105 | 160 | 143 | 0 |
| | | 15-P | 7/ 5/45 | 95 | 129 | 105 | 182 | 143 | 167 | 121 | 0 |
| | | 0 | 6/13/45 | 258 | — | 235 | 444 | — | — | — | — |
| 57 | 65 | 45-G | 7/17/45 | 125 | 157 | 69 | 91 | 125 | 190 | 131 | 0 |
| | | 45-P | 7/23/45 | 118 | 163 | 121 | 138 | 121 | 125 | 125 | 0 |
| | | 0 | 7/ 5/45 | 286 | 308 | 400 | 500 | 364 | 348 | 286 | 16 |
| 58 | 63 | 25-G | 9/ 9/45 | 95 | 133 | 170 | — | 111 | 178 | 111 | 0 |
| | | 25-P | 9/17/45 | 80 | 200 | 143 | — | 149 | 200 | 149 | 0 |
| | | 0 | 6/29/45 | 580 | — | — | — | — | — | — | — |
| 59 | 17 | 65-G | 7/20/45 | 74 | 190 | 145 | 157 | 129 | 235 | 69 | 21.4 |
| | | 65-P | 7/26/45 | 42 | 133 | 93 | 163 | 138 | 258 | 133 | 16.5 |
| | | 0 | 7/ 1/45 | — | — | — | — | 422 | — | — | — |
| 60 | 50 | 70-G | 5/22/45 | 74 | — | 125 | 154 | 125 | 133 | 186 | 0 |
| | | 70-P | 5/28/45 | 75 | — | 118 | 143 | 154 | 178 | 100 | 0 |
| | | 0 | 4/28/45 | — | — | — | 286 | — | — | — | — |
| 61 | 54 | 50-G | 5/19/45 | 83 | 200 | 83 | 222 | 182 | 228 | — | 0.3 |
| | | 50-P | 5/25/45 | 105 | 216 | 167 | 205 | 174 | 235 | — | 2.6 |
| | | 0 | 4/12/45 | — | — | — | — | — | — | 382 | — |

TABLE I—*Continued*

| Patient | Age | Units, Dose | Date | Blood Sugar Curve | | | | | | | Gm. Sugar 24 Hours' Urine |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 7:00 a.m. | 9:00 a.m. | 11:00 a.m. | 1:00 p.m. | 4:00 p.m. | 7:00 p.m. | 11:00 p.m. | |
| 61 | 54 | 70-G | 7/30/45 | 118 | 95 | 129 | 143 | 95 | 105 | 124 | 20 |
| | | 70-P | 7/23/45 | 178 | 308 | 182 | 182 | 148 | 222 | 114 | 3.2 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 62 | 76 | 45-G | 5/27/45 | 77 | 160 | 108 | 167 | 114 | 163 | 108 | 0 |
| | | 45-P | 5/22/45 | 138 | 200 | 167 | 200 | 190 | 211 | 211 | 0.9 |
| | | 0 | 4/ 3/45 | 242 | 276 | 276 | 286 | 222 | 308 | 267 | 4.6 |
| 63 | 68 | 25-G | 10/16/44 | 111 | 174 | 111 | 105 | 87 | 125 | — | — |
| | | 25-P | 9/19/44 | 62 | 90 | 110 | 150 | 148 | 172 | — | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 64 | 65 | 80-G | 3/29/45 | 78 | 170 | 200 | 211 | 143 | 157 | 93 | 0 |
| | | 80-P | 3/19/45 | 95 | 140 | 222 | 222 | 120 | 382 | 145 | 0 |
| | | 0 | 2/25/45 | — | — | 388 | — | — | — | — | — |
| 65 | 41 | 65-G | 4/30/45 | 60 | — | 103 | 108 | 60 | 100 | 66 | — |
| | | 65-P | 4/10/45 | 151 | — | 222 | 267 | 242 | 320 | 276 | 13.1 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 66 | 50 | 75-G | 4/17/45 | 129 | — | 125 | 195 | 105 | 174 | 118 | 0 |
| | | 75-P | 2/21/45 | 105 | — | 216 | 258 | 242 | 222 | 151 | 16.8 |
| | | 0 | 1/23/45 | — | — | — | — | 290 | — | — | — |
| 67 | 65 | 35-G | 2/15/45 | 103 | — | — | 154 | 103 | 149 | 103 | 0 |
| | | 35-P | 2/10/45 | 70 | — | — | 95 | 105 | 250 | 134 | 0 |
| | | 0 | 1/19/45 | 276 | — | — | — | — | 258 | — | — |
| 68 | 69 | 25-G | 5/10/45 | 105 | — | 118 | 200 | 95 | 157 | 118 | 0 |
| | | 25-P | 5/ 2/45 | 77 | — | 222 | 178 | 125 | 190 | 276 | 0 |
| | | 0 | 4/17/45 | — | — | — | — | — | 333 | — | — |
| 69 | 75 | 45-G | 7/11/45 | 167 | 167 | 118 | 121 | 69 | 148 | 111 | 0 |
| | | 45-P | 7/19/45 | 80 | 250 | 118 | 222 | 174 | 267 | 200 | 0 |
| | | 0 | 6/22/45 | 477 | 400 | 400 | 500 | 297 | 400 | 348 | 40 |

TABLE I—*Continued*

| Patient | Age | Units, Dose | Date | Blood Sugar Curve | | | | | | | Gm. Sugar 24 Hours' Urine |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 7:00 a.m. | 9:00 a.m. | 11:00 a.m. | 1:00 p.m. | 4:00 p.m. | 7:00 p.m. | 11:00 p.m. | |
| 70 | 68 | 35-G | 7/24/45 | 97 | — | 151 | 157 | 129 | 154 | 69 | 1.0 |
| | | 35-P | 7/30/45 | 121 | — | 161 | 148 | 111 | 174 | 95 | 0 |
| | | 0 | 7/ 5/45 | 308 | — | — | 333 | 286 | 383 | 267 | — |
| 71 | 55 | 35-G | 7/ 3/45 | 87 | 143 | 111 | 195 | 100 | 100 | 86 | 7.2 |
| | | 35-P | 6/26/45 | 103 | 154 | 122 | 228 | 213 | 182 | 105 | 21 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 72 | 71 | 40-G | 4/24/45 | 105 | 143 | 60 | 114 | 60 | 186 | 85 | 0 |
| | | 40-P | 4/16/45 | 85 | 133 | 129 | 149 | 163 | 157 | 91 | 0 |
| | | 0 | 4/ 5/45 | 228 | 250 | 228 | 242 | 228 | 235 | 182 | 4.0 |
| 72 | 71 | 25-G | 7/ 3/45 | 167 | 138 | 158 | 200 | 105 | 93 | 95 | 0 |
| | | 25-P | 7/11/45 | 81 | 143 | 160 | 100 | 67 | 124 | 91 | 0 |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 73 | 28 | 40-G | 11/28/44 | 125 | 194 | 170 | — | — | 288 | 182 | 2.2 |
| | | 40-P | 11/20/44 | 77 | 98 | 124 | — | — | 163 | 122 | 4.6 |
| | | 0 | 11/ 4/44 | 252 | — | — | — | — | — | — | — |
| 73 | 28 | 20-G | 10/ 2/45 | 83 | 178 | 74 | 125 | 111 | 128 | 111 | 0 |
| | | 20-P | 9/24/45 | 125 | 235 | 129 | 121 | 188 | 200 | 178 | 0 |
| | | 0 | — | — | — | — | — | — | — | — | 0 |
| 74 | 51 | 75-G | 8/15/45 | 105 | 167 | 186 | 250 | 80 | 180 | 145 | 0 |
| | | 75-P | 8/21/45 | 211 | 333 | 308 | 348 | 332 | 320 | 297 | 44 |
| | | 0 | 8/ 6/45 | — | — | — | — | 444 | 382 | — | — |
| 75 | 35 | 40-G | 7/27/45 | 111 | 228 | 93 | 114 | 111 | 174 | 160 | 0 |
| | | 40-P | 7/23/45 | 83 | 114 | 69 | 200 | 74 | 105 | 83 | 0 |
| | | 0 | 4/22/45 | — | — | — | — | — | 382 | — | — |
| 76 | 26 | 15-G | 2/27/45 | 103 | 133 | 73 | 125 | 86 | 116 | 138 | 0 |
| | | 15-P | 2/ 8/45 | 103 | 111 | 89 | 111 | 103 | 109 | 163 | 1.8 |
| | | 0 | 1/16/45 | 167 | 235 | 216 | — | 174 | 170 | — | 4.1 |

TABLE I—*Continued*

| Patient | Age | Units, Dose | Date | Blood Sugar Curve | | | | | | | Gm. Sugar 24 Hours' Urine |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 7:00 a.m. | 9:00 a.m. | 11:00 a.m. | 1:00 p.m. | 4:00 p.m. | 7:00 p.m. | 11:00 p.m. | |
| 77 | 37 | 40-G | 7/ 3/45 | 125 | 143 | 114 | 125 | 77 | 129 | 111 | 4.0 |
| | | 40-P | 7/ 7/45 | 83 | 200 | 97 | 149 | 67 | 133 | 124 | 0 |
| | | 0 | 6/18/45 | 320 | 400 | — | 422 | 242 | 422 | 242 | 32 |
| 78 | 64 | 20-G | 7/24/45 | 134 | — | 186 | 235 | 143 | 182 | 160 | 0 |
| | | 20-P | 7/30/45 | 125 | — | 97 | 205 | 148 | 200 | 134 | 0 |
| | | 0 | 7/ 7/45 | — | — | — | — | 325 | — | — | 14.2 |
| 79 | 54 | 45-G | 9/17/45 | 161 | 89 | 133 | — | — | — | 174 | — |
| | | 45-P | 9/22/45 | 222 | 190 | 222 | — | — | — | 235 | — |
| | | 0 | 9/12/45 | — | — | — | — | — | 348 | — | — |
| 80 | 44 | 45-G | 11/20/44 | 82 | 208 | 75 | 60 | 59 | 105 | 59 | 0 |
| | | 45-P | 11/13/44 | 75 | 193 | 176 | 251 | 146 | 172 | 81 | 3.95 |
| | | 0 | 10/20/44 | — | — | — | — | 230 | — | — | — |
| 81 | 35 | 35-G | 11/21/45 | 95 | 71 | 77 | 108 | 80 | — | — | — |
| | | 35-P | 11/12/45 | 111 | 205 | 149 | 190 | 133 | — | — | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 82 | 72 | 20-G | 10/ 5/45 | 93 | 160 | 100 | 143 | 89 | 151 | 100 | — |
| | | 20-P | 9/14/45 | 83 | 200 | 111 | 154 | 114 | 160 | 71 | — |
| | | 0 | — | — | — | — | — | — | — | — | — |
| 83 | 75 | 35-G | 8/ 8/45 | 83 | 174 | 67 | 133 | 74 | 130 | 110 | 0 |
| | | 35-P | 8/12/45 | 69 | 182 | 125 | 216 | 125 | 137 | 165 | 0 |
| | | 0 | 6/28/45 | 211 | — | 382 | 571 | 477 | 600 | 570 | 30 |
| 84 | 61 | 20-G | 5/16/45 | 182 | 186 | — | 138 | 222 | 167 | 145 | 0 |
| | | 20-P | 5/ 8/45 | 125 | 228 | — | 242 | 138 | 222 | 242 | 0 |
| | | 0 | — | — | — | — | — | — | — | — | — |

urinary output of sugar for the 84 patients studied in 97 hospital admissions while they were receiving: (a) globin insulin with zinc, (b) protamine zinc insulin in the same dosage, and (c) no insulin. From these data, composite blood sugar curves were made from the averages of blood sugars at each of the seven points of time and with each form of treatment for all the cases. These averages of the blood sugars, with the averages of the urinary sugar, are given in table 2.

TABLE II

Composite blood sugar curves and average 24-hour urinary dextrose excretion for 84 patients on 97 admissions on equal doses of globin insulin, protamine zinc insulin, and no insulin

| Form of Insulin | Blood Sugar (mg. %) | | | | | | | Gm. Dextrose Sugar in 24 Hours' Urine |
|---|---|---|---|---|---|---|---|---|
| | 7 a.m. | 9 a.m. | 11 a.m. | 1 p.m. | 4 p.m. | 7 p.m. | 11 p.m. | |
| Globin | 109 | 159 | 125 | 161 | 116 | 157 | 131 | 1.9 |
| Protamine Zinc | 108 | 178 | 149 | 183 | 150 | 194 | 140 | 5.6 |
| None | 254 | 275 | 253 | 325 | 269 | 317 | 274 | 20.1 |

From these averages as shown in figure 1, it is evident that the blood sugar curve approached the normal trend more nearly with globin insulin than with protamine zinc insulin. Although the average fasting blood sugar was the same with the two forms, blood sugar levels were higher with protamine zinc insulin at all other times tested. Although the blood sugar

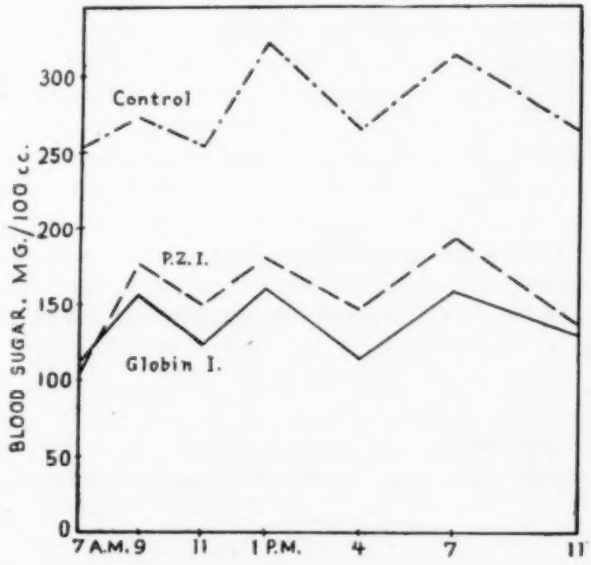


FIG. 1. Composite blood sugar curves based on 97 case comparisons obtained on 84 patients while receiving: (1) no insulin (Control), and equal doses of (2) globin insulin (Globin I.) and (3) protamine zinc insulin (P. Z. I.).

returned to normal before lunch, before supper and before midnight with globin insulin it was in the hyperglycemic range at these times with equal doses of protamine zinc insulin. The post-prandial rises were higher with protamine zinc insulin than with globin insulin.

These average blood sugar values were analyzed statistically by means of the "t" test in order to determine whether the differences between the values obtained with globin insulin and with protamine zinc insulin were significant. The "t" test and other statistical methods referred to in this paper are described in standard texts such as "Statistical Methods," 4th edition, 1946, by G. W. Snedecor, Iowa State College Press, Ames, Iowa. The values for "t" for the various time intervals from 7:00 a.m. to 11:00 p.m. were respectively, 0.188, 2.32, 3.39, 2.44, 4.17, 4.32 and 1.11. A value for "t" greater than 1.97 indicates that the probability is less than 1 in 20 that the two values being compared are merely chance variations, and the difference is considered significant; "t" greater than 2.6 indicates a probability of less than 1 in 100 that the two values are chance variations, and such a difference is regarded as highly significant.

It is seen that the average blood sugar values for globin insulin and protamine zinc insulin were not significantly different at 7:00 a.m. and 11:00 p.m. At each other time the average blood sugar level was significantly lower for globin insulin than for protamine zinc insulin; the "t" values indicate that these differences are not due to chance alone.

The data were also given a comprehensive treatment by an analysis of variance. The variation due to three major factors: (1) the difference between the two types of insulin; (2) the collection of blood samples at seven different time intervals; and (3) the difference between patients, was segregated and expressed as a variance. Each of these three variances was divided in turn by the variance due to experimental error and the three respective variance ratios or F values were found to be (1) 62.52, (2) 32.18, and (3) 4.16. These figures were then compared with their corresponding values in tables of distribution of F to determine whether they were significant. The large F value of 62.52 shows beyond question that globin insulin controlled the blood sugar better than protamine zinc insulin. As was to be expected, blood sugars were significantly different at various times of the day, and patients differed significantly from each other.

The averages of the 24-hour urinary sugar analyses were as follows: 1.9 grams with globin insulin and 5.6 grams with protamine zinc insulin. The average glycosuria of these patients was controlled better with globin insulin than with protamine. It is of significance that this occurred with the same preparation which gave more nearly normal control of the blood sugar curve.

The 24-hour urinary sugar data were also analyzed on the basis of frequency of incidence of glycosuria. Data were obtained on 76 patients with both globin insulin and protamine zinc insulin. Among these 76 patients, measurable glycosuria occurred in 33 cases with protamine zinc insulin and

20 cases with globin insulin. The chi-square was 4.9 with a value of P less than 0.05, that is, the probability is less than 1 in 20 that this difference would arise by chance alone; the incidence of glycosuria was, therefore, significantly less with globin insulin than with protamine zinc insulin under the conditions of these studies.

Likewise, of the 76 patients, there were 19 having glycosuria of more than 5 grams in 24 hours when protamine zinc insulin was used and only nine when globin insulin was used. The value for chi-square was 4.38, corresponding to a value for P of less than 0.05. The incidence of glycosuria of more than 5 gm. in 24 hours was, therefore, significantly lower with globin insulin than with protamine zinc insulin.

If the cases showing no glycosuria with either insulin preparation are eliminated, the differences are even more striking. Thus, a total of 35 cases had glycosuria with either globin insulin or protamine zinc insulin or both. Of these, 33 had glycosuria with protamine zinc insulin and 20 with globin insulin. In other words, there were only two cases having glycosuria with globin insulin that did not also have glycosuria with protamine zinc insulin. The value of chi-square for these data is 13, corresponding to P of less than 0.01, which indicates a highly significant difference in the results.

Similarly, of 20 cases in which there was glycosuria of 5 gm. per 24 hours or more, 19 had this degree of glycosuria with protamine zinc insulin and only nine with globin insulin. The chi-square value is 11.7, P is less than 0.01, and the difference is highly significant.

## Illustrative Cases

In the group of patients with comparable curves on equal doses of the two preparations, there were many in whom there was clear evidence that globin insulin was superior to protamine zinc insulin in controlling the blood sugar curve, while in a few cases the converse was found. In some patients, the curves on the two preparations were very similar. In other patients the curves showed great difference in the times at which the two preparations were most effective. Since the curves of all the cases cannot be produced here, only samples of the various trends will be shown.

1. S. P., Case 62, a 76 year old colored woman who had been a known diabetic for 15 years was admitted with back pain, polydipsia, polyuria, nocturia and hypertension. With no insulin, a blood sugar curve was high at all hours, with rises after each meal (figure 2). Protamine zinc insulin, 15 units, was started and raised to 45 units before the 24-hour urinary sugar fell below 5 gm. and the fasting blood sugar approached normal. A curve on the fourth day on this dose had all levels near 200 mg. per cent except the fasting and pre-lunch specimens. Globin insulin, 45 units, was then used instead of the protamine zinc insulin. On the fourth day after the change to globin insulin, a curve showed normal blood sugars before each meal and midnight, with rises to only 160 to 167 mg. per cent after each of the three meals. Thus, in this patient, better control occurred with globin insulin.

2. Y. I., Case 37, a 53 year old Japanese male, with known diabetes for five years, had mild hypertension and chronic nephritis. A curve after 19 days on 25 units of

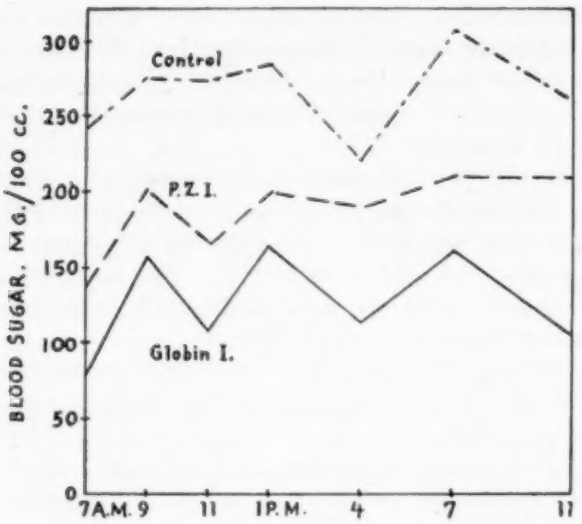


FIG. 2. Blood sugar curves of a patient (S. P., Case 62) receiving no insulin (Control), and, in turn, 45 units each of globin insulin (Globin I.) and protamine zinc insulin (P. Z. I.). Globin insulin gave better control.

globin insulin revealed blood sugars of 136 mg. per cent at 7:00 a.m. (fasting) and 77 at 4:00 p.m. At other hours tested the blood sugar was above normal, 160 to 207 mg. per cent (figure 3). After nine days on 25 units of protamine zinc insulin, the blood sugar was in the lower ranges of normal (85 to 95 mg. per cent) at each hour tested except for a rise to 133 mg. per cent after lunch and a fall to 51 mg. per cent at 11:00 p.m. Although this indicated better control of the blood sugar curve with protamine zinc insulin, a few days later the patient began to complain of mild clinical reactions to the protamine zinc insulin in the late afternoon even when the dose was dropped to 20 units. With doses of 15 to 20 units of globin insulin, he felt better, according to his statement and was discharged on this régime. Curves on these lower doses of globin insulin also indicated hyperglycemia after breakfast and supper, with reasonably good control of the blood sugar at other times.

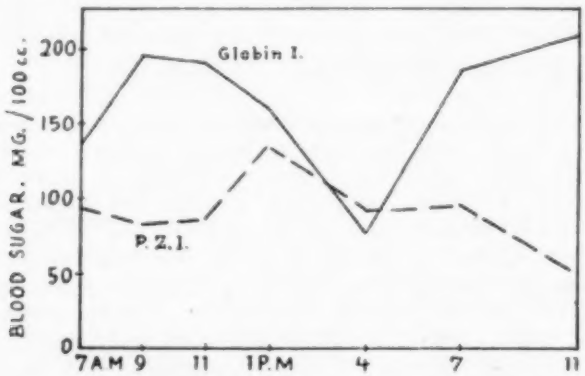


FIG. 3. Blood sugar curves of a patient (Y. I., Case 37), receiving, in turn, 25 units each of globin insulin and protamine zinc insulin. The latter provided a better curve, but induced mild clinical reactions not experienced with globin insulin.

3. J. M., Case 52, a 63 year old white male was admitted with gangrene of a toe and found to have diabetes mellitus with a blood sugar curve which was high at all hours when he was not receiving any insulin. After correction of the acute condition and rising doses of protamine zinc insulin a curve on the sixth day with 30 units daily showed a smooth curve which was normal throughout (figure 4). Eight days after being changed to 30 units daily of globin insulin a curve showed blood sugars of 125 to 211 mg. per cent. It would seem that in this instance the use of protamine

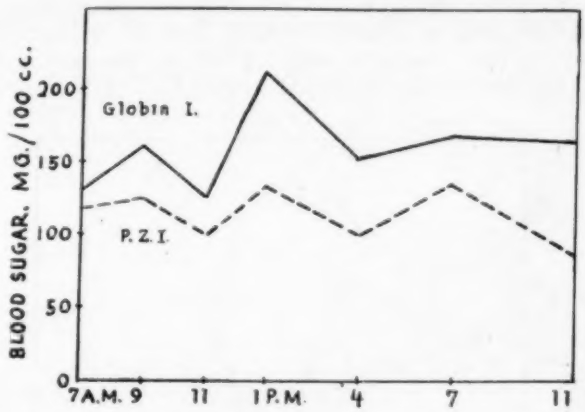


FIG. 4. Blood sugar curves of a patient (J. M., Case 52) showing better control with 30 units of protamine zinc insulin than with 30 units of globin insulin.

zinc insulin was preferable. On two subsequent occasions comparisons were made between the two preparations with dosages of 35 units and 20 units. From the data as shown in table 1 protamine zinc insulin might be considered preferable in this case.

4. A. H., Case 36, a 60 year old white woman, was found to be a mild diabetic after suffering an episode of hemiplegia. A blood sugar curve after seven days on 20 units of protamine zinc insulin closely resembled that made after nine days on 20 units of globin insulin (figure 5). However, the levels of 70 and 68 mg. per cent occurring after supper and at 11:00 p.m. with protamine zinc insulin were lower than one likes to see in an elderly diabetic patient. Within the next two months, this patient's requirement for insulin gradually fell to zero. This case is representative

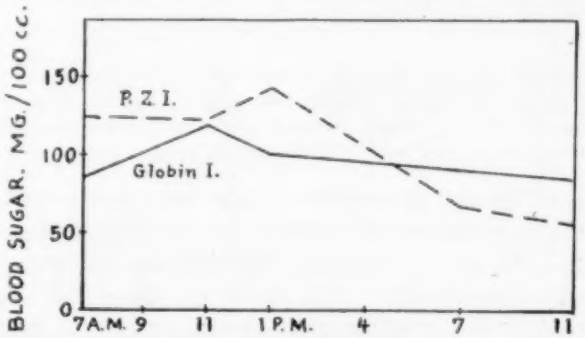


FIG. 5. Blood sugar curves of a patient (A. H., Case 36) receiving, in turn, 20 units each of globin insulin and protamine zinc insulin. Good control was obtained with either preparation.

of a group in which either form of insulin seems just about as effective as the other; this group is generally composed of rather mild diabetic patients, needing less than 25 units of insulin daily with a measured diet.

5. A. G., Case 26, a 36 year old severe diabetic patient, is illustrative of a group in which two forms of insulin showed striking differences in the degree of effectiveness at different hours. A known diabetic for three years, she developed acidosis and coma after omitting her usual daily dose of 30 units of protamine zinc insulin. Following correction of this her daily need for insulin was found to have increased greatly. One month after admission and the fifth day on 80 units of protamine insulin, her blood sugar curve showed a fasting level of 40 mg. per cent, rising rapidly throughout the entire day to a peak of 382 mg. per cent at 7:00 p.m. and falling only to 235 mg. per cent by 11:00 p.m. (figure 6). On the sixth day after the

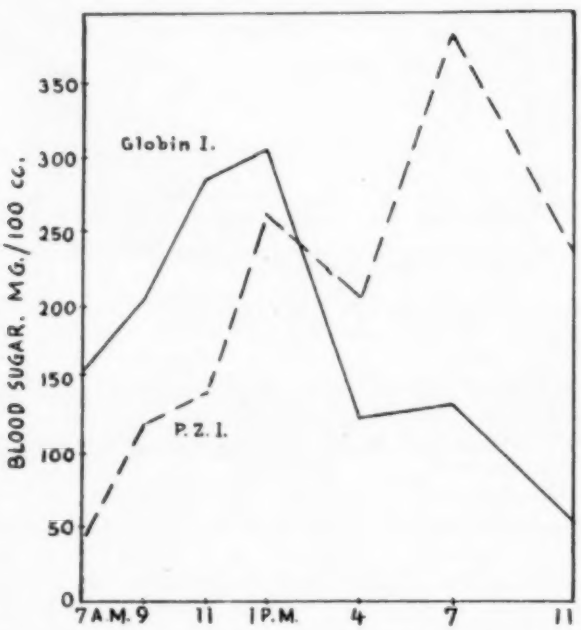


FIG. 6. Blood sugar curves of a patient (A. G., Case 26) receiving, in turn, 80 units each of globin insulin and protamine zinc insulin. Neither preparation gave good control. Note the different timing of effectiveness of the two preparations.

protamine zinc insulin was changed to 80 units of globin insulin, the curve showed wide variations from a low level of 52 mg. per cent at 11:00 p.m. to 308 mg. per cent at 1:00 p.m. The only really normal levels occurred with protamine zinc insulin after breakfast and before lunch, and with globin insulin before supper and after supper.

As examples of the fact that globin insulin may give better control of the diabetic state than protamine zinc insulin when large doses of insulin are required, figures 7, 8 and 9 show curves of three patients receiving 80, 75 and 70 units of insulin respectively. This result is contrary to statements made by some authors, who thought that globin insulin might be unsatisfactory for patients with severe diabetes needing more than 40 units of insulin daily.

Not considering the comparison of the two forms of insulin in equal doses

we have studied in the hospital 192 patients treated with globin insulin, although not all of these were available for a sufficient period to allow determination of the possibility of adequate control. Of the whole group, 88 (45.8 per cent) were well controlled, with no blood sugars above 175 mg. per cent; 39 (20.3 per cent) were moderately well controlled, with some blood sugars between 175 and 200 mg. per cent; and 65 (34 per cent) were inadequately controlled, with at least one blood sugar above 200 per cent. Thus, there were 127 (66.1 per cent) well controlled or moderately well con-

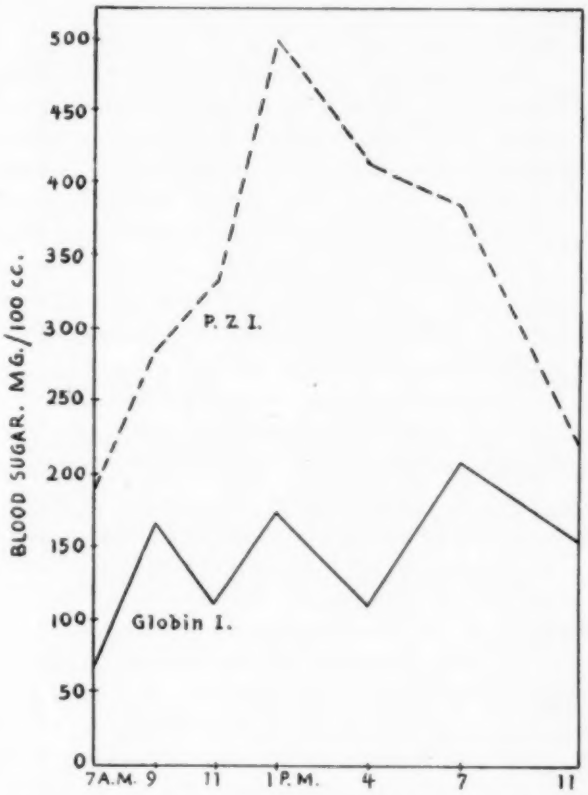


FIG. 7. Blood sugar curves for a patient (G. D., Case 21) showing much better control with 80 units of globin insulin than with 80 units of protamine zinc insulin.

trolled by globin insulin in the dosages used. Of the other 65 patients, an unknown number might have been so controlled had a better opportunity been afforded or if the rather arbitrary and elaborate criteria for control had not been adhered to so strictly. Generally these were patients who refused advice or care.

The statement has been made that globin insulin does not continue to be effective throughout the night to a degree capable of controlling the blood sugar during the night and before breakfast or to control the blood sugar

during the morning after breakfast. In our experience this difficulty has not been very common. Generally in the patients with comparable curves we have found that the fasting blood sugar, late night blood sugar, and the blood sugars during the morning after breakfast have been controlled fully

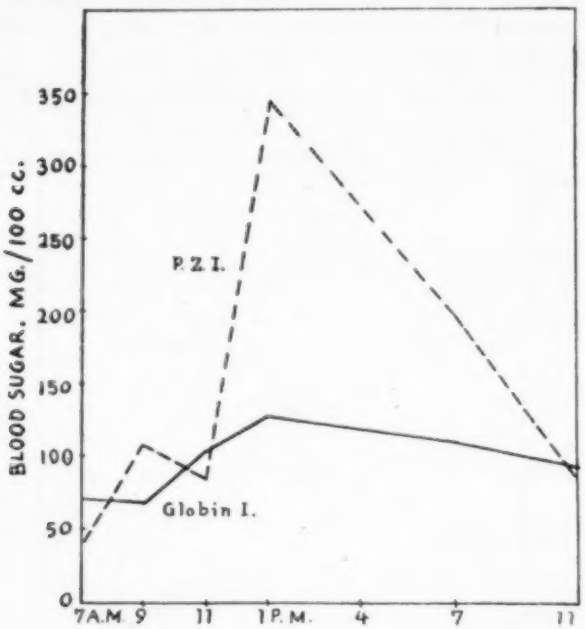


FIG. 8. Blood sugar curves of a patient (S. H., Case 30) showing good control with 75 units of globin insulin but poor control with 75 units of protamine zinc insulin.

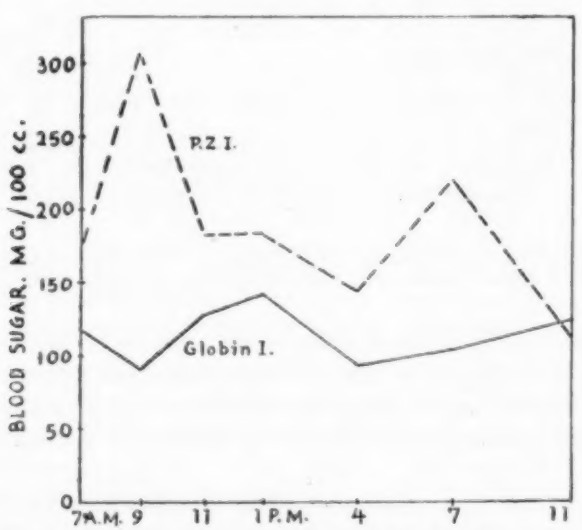


FIG. 9. Blood sugar curves of a patient (M. P., Case 61) showing excellent control with 70 units of globin insulin, but poor control with 70 units of protamine zinc insulin.

as well or better with globin insulin than with protamine zinc insulin. As indicated by the averages in table 2 and figure 1 the fasting and 11:00 p.m. blood sugar levels were practically identical with the two preparations, and the averages for the 9:00 a.m. blood sugar level taken an hour after breakfast and for the 11:00 a.m. blood sugar level taken just before lunch were more nearly normal with globin insulin.

## Insulin Reactions

A record was kept of three types of reactions to insulin: (a) systemic, (b) purely chemical, and (c) local. In the group of 84 hospitalized patients with blood sugar curves compared on 97 occasions while getting the same dosage of the two preparations, there was only one mild systemic reaction while the patients were getting globin insulin, and five systemic reactions while they were getting protamine zinc insulin (three mild, two moderate).

Taking blood sugars of 70 mg. per cent and under as indicating hypoglycemia from a purely chemical viewpoint, there were 24 instances of this kind while the patients were getting globin insulin and 26 while they were receiving protamine zinc insulin in equal doses. There were no severe local reactions while the patients in this group were receiving globin insulin and only one while they were getting protamine zinc insulin in equal doses. Minor local reactions were elicited by careful quizzing in one of these patients while he was getting protamine zinc insulin and in only two while they were getting globin insulin. This group of patients was receiving globin insulin mixed with glycerin. Formerly, while globin insulin not mixed with glycerin was being used there were a few local reactions, but these were eliminated when the glycerin preparation was substituted.

Because of systemic or chemical hypoglycemic reactions a small feeding was given from 2:30 to 3:00 p.m., in some of the more severe and fluctuating cases while globin insulin was being given, since the reactions occurred shortly after this time. In this way the reactions were obviated. This was not needed by any of the patients whose blood sugar curves were compared on equal doses of the two preparations. Likewise, a small feeding is often necessary at about 9:00 p.m. for some patients while they are receiving protamine zinc insulin and occasionally when they are getting globin insulin in order to avoid nocturnal reactions. In the present group, however, this was needed by only two patients with protamine zinc insulin and one with globin insulin. These feedings were usually a meat sandwich and a glass of milk.

In the larger group of all patients given globin insulin and observed by us, severe hypoglycemic reactions have occurred only to patients who received very large overdosage, while omitting food; these patients were neglected grossly before arrival at this hospital, and similar reactions would be expected with any insulin under such conditions.

## Discussion

It appears to us from the experience gained by this comparison of the two slowly acting forms of insulin that both are satisfactory preparations in the treatment of a large percentage of diabetics. Although each form is better than the other in some patients, more of them were controlled more satisfactorily with globin insulin. The comparison we have made with equal doses of the two preparations does not show necessarily the true effectiveness of either for all cases, however, since a larger dose of one or the other, or a complementary dose of regular insulin, usually before breakfast, might have been expected to bring about a little more satisfactory control in some instances. Most of these patients were controlled as well as possible, however, by one preparation or the other under the circumstances at the time. In the literature Bauman,[1-5] Marks,[6] Duncan and Barnes,[7] Bailey and Marble,[8] Paul,[9] Greenhouse,[10, 11] Mosenthal,[12] Protas,[13] Eaton,[14] Martin, Simonsen and Homann,[15] Margolin,[16] Ricketts,[17] Trasoff, Borden and Mintz,[18] Jackson and McIntosh,[19] Irwig,[20] Reiner, Lang, Irvine, Peacock and Evans,[21] Andrews and Groat,[34] Levitt and Schaus,[35] Colwell [36] and others have reported that the use of globin insulin was satisfactory to them or their data indicated that this might be so. Page and Bauman [4] found that cutaneous reactions to globin were less frequent than to protamine in both allergic and nonallergic patients. Lawrence,[22] Murphy,[23] Peck and Schechter,[24] Marble,[25] MacBryde and Reiss,[26] Jordan,[27] MacBryde,[28] DelFierro and Sevringhaus,[29] Malins,[30] concluded that there was no advantage or that there even was objection to the use of globin insulin except for patients who were sensitive to protamine zinc insulin. Some authors, for example, MacBryde and H. K. Roberts,[31] think that confusion results from the introduction of this additional preparation and that only unmodified or crystalline insulin and protamine zinc insulin are needed.

There is a trend on the part of some authors (Colwell and Izzo,[32] Adlersberg and Dolger,[33] and some others cited above) to use mixtures of crystalline insulin and protamine zinc insulin, most popularly 2 to 1 and 3 to 1. A mixture of these two preparations in the bottle or in the syringe, with the ratio varying according to daily needs, may be effective in the hands of very conscientious and intelligent patients, but is unsatisfactory for many patients. We believe that some authors are over-emphasizing the necessity of such a method in a large number of cases. We still think that the use of a single, long-acting insulin is preferable whenever satisfactory control can be attained and that this is possible in a very large percentage of cases with either globin insulin or protamine zinc insulin. Since the preparation of choice for any patient is the one which works best for that individual, globin insulin, protamine zinc insulin, or each should be tried before using mixtures of insulins or unusual timing of insulin administration.

Our experience with handling the mixtures of protamine and regular insulins has shown that these may be very confusing to many physicians or patients even in a teaching hospital.

In each of our very difficult cases in which very large doses of insulin were necessary or in which the diabetic state was very labile, best results have been obtained often by giving two doses of globin insulin (about 70 per cent of the needed amount before breakfast, the rest at 3:00 p.m.). This has been much simpler for both the patients and physicians than treatment with various mixtures of two or three forms of insulins.

The infrequent hypoglycemic reactions to globin insulin may be controlled usually by a small midafternoon feeding. Local reactions to globin insulin with glycerin have been insignificant in this group of patients.

## Conclusions

Globin insulin (prepared with zinc and glycerin) is a safe and useful preparation for the treatment of diabetic patients. Globin insulin controls the blood sugar curve and glycosuria in a more nearly normal way in more cases than an equal dose of protamine zinc insulin. Globin insulin as now prepared with glycerin is free of significant local reactions or allergy. The tendency to midafternoon hypoglycemia with globin insulin is preferable to nocturnal reactions which are likely to be severe with protamine zinc insulin. The majority of patients with diabetes who require insulin can be adequately controlled by a single dose of either globin insulin or protamine zinc insulin.

*Note:* We are indebted to the following Residents on the Diabetic Service for their persistence and enthusiastic coöperation in making possible this investigation: Drs. S. W. Kirstein, W. M. Goodman, M. H. Lepper, A. B. Coleman, F. Wilhelm, Wm. Kurstin, S. D. Loube, R. W. Merkle, W. F. Oliver, S. Kling, W. S. Schweikert, and B. A. Fitzgerald, and to the many others who helped in any way.

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# FURTHER OBSERVATIONS ON BLOOD GROUPING IN POLIOMYELITIS *

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## Introduction

The selective distribution of paralytic cases of poliomyelitis is well recognized but no explanation of the phenomenon has been offered which has found general acceptance. Epidemiological data are interpreted by some to suggest that the haphazard spread of paralysis is caused by limiting factors germane to the mode of virus dissemination. Other observers, mostly on clinical grounds, believe that the paralytic case represents only the rare accident in a long chain of abortive infections, occurring in especially predisposed individuals. Although the available knowledge does not permit a clear decision, the weight of evidence would seem to rest with the second hypothesis.

The predisposing factors that may contribute to the severe involvement of the central nervous system are probably exogenous as well as endogenous. Some of the former, such as fatigue, tonsillectomy and insolation, were studied experimentally and found to be instrumental in opening up peripheral portals of entry or breaking down neural defense mechanisms. The problem of endogenous predisposition, on the other hand, depending as it does upon the constitutional make-up and hereditary stigmatization of the individual, is too complex to lend itself to profitable experimentation at this time. Certainly, earlier attempts to secure an experimental basis for the significance of endocrine dysfunction or vitamin deficiency have failed to provide an unequivocal answer. A purely empirical approach, however, is possible by examining the distribution of blood group genes among poliomyelitis patients as compared with suitable control populations.

## Experimental

Since 1930, when blood grouping in poliomyelitis was begun, a considerable amount of information has accumulated over a period of years. Yet proper evaluation of the data is hampered for several reasons. In the first place, much of the published material is concerned with small series which lack statistical significance. Moreover, in some instances paralytic and non-paralytic cases, without distinction, were tabulated together; in others, the series included admittedly a majority of non-paralytic patients.

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The necessity for separating the two types of cases is self-evident from the nature of the problem. Selection of the control material, finally, has not always met the requirements as to geographical and chronological homogeneity as postulated by Schiff.[1] In table 1 we have brought together the figures of 10 series published by various investigators[2-12] from different parts of the world.

TABLE I

Blood Grouping in Poliomyelitis

| Series | Author | Locality | Year | Cases | Number | O | A | B | AB |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | (%) | (%) | (%) | (%) |
| I | Grooten and Kossovitch | France | 1930 | Poliomyelitis (all cases) | 78 | 29.1 | 56.4 | 14.5 | 0 |
| | Grooten and Kossovitch | France | 1930 | Normal | 100 | 37.7 | 39.6 | 16.9 | 5.8 |
| II | Jungeblut and Smith | N. Y. City | 1916 | Poliomyelitis (paralytic) | 208 | 51.9 | 32.2 | 6.7 | 8.2 |
| | Ottenberg | N. Y. City | 1921 | Normal | 286 | 44.0 | 42.0 | 12.0 | 2.0 |
| III | Jungeblut and Smith | N. Y. City | 1931 | Poliomyelitis (all cases) | 343 | 42.5 | 39.9 | 12.5 | 5.1 |
| | Jungeblut and Smith | N. Y. City | 1931 | Poliomyelitis (paralytic) | 236 | 46.6 | 38.1 | 10.6 | 4.7 |
| | Jungeblut and Smith | N. Y. City | 1931 | Poliomyelitis (abortive) | 107 | 33.6 | 43.9 | 16.8 | 5.6 |
| | Jungeblut and Smith | N. Y. City | 1931 | Normal | 1000 | 45.6 | 35.7 | 14.0 | 4.7 |
| | Tiber | N. Y. City | 1925/29 | Normal | 10,000 | 45.6 | 36.4 | 13.5 | 4.5 |
| IV | Shaw et al. | San Francisco | 1931 | Poliomyelitis (all cases) | 100 | 57.0 | 37.0 | 6.0 | 0 |
| | Shaw et al. | San Francisco | 1931 | Normal | 100 | 43.0 | 43.0 | 11.0 | 3.0 |
| V | Blotevogel and Blotevogel | Germany | 1928/33 | Poliomyelitis (paralytic) | 366 | 53.0 | 34.7 | 6.8 | 5.5 |
| | Blotevogel and Blotevogel | Germany | 1928/33 | Normal | 3500 | 41.4 | 43.4 | 10.1 | 5.1 |
| VI | Hatzky | Germany | 1933 | Poliomyelitis (all cases) | 131 | 38.2 | 43.5 | 16.8 | 1.5 |
| | Hatzky | Germany | 1933 | Normal | 9111 | 43.4 | 46.6 | 6.8 | 3.2 |
| VII | Madsen et al. | Denmark | 1934 | Poliomyelitis (all cases)* | 1118 | 43.4 | 41.7 | 10.0 | 4.9 |
| | Madsen et al. | Denmark | 1934 | Normal | 19,417 | 42.6 | 42.4 | 11.4 | 3.6 |
| VIII | Erb et al. | Canada | 1938 | Poliomyelitis (all cases) | 703 | 48.4 | 37.7 | 11.5 | 2.4 |
| | Erb et al. | Canada | 1938 | Poliomyelitis (paralytic) | 427 | 50.8 | 37.5 | 9.8 | 1.9 |
| | Erb et al. | Canada | 1938 | Poliomyelitis (abortive) | 276 | 44.6 | 38.0 | 14.1 | 3.3 |
| | Erb et al. | Canada | 1938 | Normal | 1000 | 44.7† | 40.8 | 11.6 | 2.9 |
| IX | Kleinschmidt | Germany | 1939 | Poliomyelitis (all cases) | 309 | 41.8 | 45.0 | 9.4 | 2.6 |
| | Kleinschmidt | Germany | 1939 | Poliomyelitis (paralytic) | 211 | 46.0 | 43.6 | 8.1 | 2.4 |
| | Kleinschmidt | Germany | 1939 | Poliomyelitis (abortive) | 98 | 32.7 | 51.0 | 12.2 | 4.1 |
| | Kleinschmidt | Germany | 1939 | Normal | 1100 | 42.0 | 44.5 | 11.0 | 2.5 |
| X | Fanconi | Switzerland | 1944 | Poliomyelitis (all cases) | 507 | 37.3 | 53.5 | 7.0 | 5.0 |
| | Fanconi | Switzerland | 1944 | Normal | 1000 | 40.2 | 48.0 | 9.2 | 2.6 |

* This series included only 47 paralytic cases.
† Corrected figure (personal communication).

An inspection of table 1 will show that in five series (II, III, V, VIII, IX) in which paralytic patients are listed, group B occurs with lesser frequency among the poliomyelitis patients than among the corresponding normal control individuals. The difference is not very great but recurs consistently in each of the five series mentioned. On the other hand, in the known abortive cases (series III, VIII, IX) group B occurs with a slightly higher frequency although only a few such comparisons are available. The comparison of unclassified cases, including an unknown percentage of paralyzed and abortive cases, may therefore be misleading. However, when

unclassified cases (series I, IV, VI, VII, X) are considered, with this reservation in mind, the diminished incidence of group B among the poliomyelitis patients appears again in four series (I, IV, VII, X) but is generally of smaller magnitude; one series (VI) shows an increase of group B for the poliomyelitis patients as compared with the normal controls. The deficit arising from this B shortage is mostly compensated for by an increased incidence of group O (II, IV, V, VII, VIII, IX), especially when paralyzed cases are considered; in one series (III) the increment is spread between groups O and A, while in the two remaining series (I, X) it is chiefly confined to group A. Variations in blood group AB are not being considered here because the figures are too small to warrant separate discussion.

Further interest was added when Kleinschmidt [2] first segregated the subgroups $A_1$ and $A_2$, which comprise blood group A, in poliomyelitis patients. The figures recorded for paralytic cases showed a $A_1/A_2$ ratio of 1:2.5, as compared with the normal ratio of about 1:4 (Mueller and Dahr [13]). Expressed by the relation $\frac{A_2 + A_2B}{A_1 + A_1B}$, 211 paralytic cases showed an index of 0.45 against an index of 0.29 for 98 non-paralytic cases. The index for 416 normal Germans is given as 0.19 by Dahr, Offe and Weber.[14] In other words, there was a notable increase of $A_2$ at the expense of $A_1$ in the poliomyelitis patients with paralysis. The same author determined for the first time the distribution of the blood antigens M and N in poliomyelitis patients and found the type N somewhat increased over the normal frequency (N in paralyzed poliomyelitis cases = 29.33 per cent; N in normal individuals = 21.5 per cent). Kleinschmidt's final conclusions were that individuals having blood groups O, $A_2$ or factor N are predisposed to infection with paralytic poliomyelitis, whereas individuals with blood groups $A_1$, B or factor M tend to acquire the non-paralytic form of the disease.

The data to be reported in this paper are based on blood group determinations of 220 poliomyelitis patients. Groups O, $A_1$, $A_2$, B, $A_1B$ and $A_2B$ were determined for the entire series; 187 patients were furthermore typed for the $Rh_0$ factor. In addition, 116 samples of saliva from selected poliomyelitis patients with the blood groups $A_1$, $A_2$, B, $A_1B$ and $A_2B$ were examined for the absence or presence of the corresponding blood group substance. In accordance with established practice, persons having this substance in their saliva are designated "Secretors" as contrasted with "Non-secretors" who lack it. As is well known, the ability or inability to secrete group-specific substance in saliva represents a constant trait of the individual and is hereditary in character.

The series of 220 poliomyelitis patients consisted of 219 white individuals and one colored person. All but 29 cases had occurred during the 1944 epidemic of the Greater New York area; the remaining 29 persons were 1945 cases. The majority of the patients were children under 10 years of age. All were authentic cases of poliomyelitis with variable paralytic involvement, 190 cases being classified as moderate to severe and 30 as light.

None was of the abortive or non-paralytic type. The patients were hospitalized at the following institutions: New York State Reconstruction Home (172 cases); Grasslands Hospital (10 cases); Hospital for Joint Diseases (13 cases); Hospital for Special Surgery (25 cases). We are indebted to Drs. K. Landauer, G. Dalldorf, J. Blair, and P. D. Wilson for their cooperation and permission to study these cases. Our thanks are also due to Mr. R. Amado of the N. Y. State Reconstruction Home for valuable assistance in supplying necessary clinical information. The control material for the distribution of the four blood groups in normal individuals was obtained from the Blood Bank of Presbyterian Hospital, New York City. We are offering the records of a total of 20,211 normal donors, mostly residing in the Greater New York area, who were typed between November 1942 and May 1945. For further comparison of the frequencies of subgroups $A_1$ and $A_2$ among normal people there is listed a series of 1077 white individuals (N. Y. 1933–1943) published by Wiener.[15] Control material for determination of the frequency of "Secretors" and "Non-secretors" among normal individuals was obtained by typing the saliva of 111 selected normal medical students of the College of Physicians and Surgeons, Columbia University, with blood groups A, B, or AB. Additional control figures are provided by two published series of Schiff [16] and Wiener,[15] respectively.

The tests were carried out by typing freshly collected unknown red cells against known group A II (anti-B) and group B III (anti-A) human sera by the open well slide technic. The sera were obtained from Dr. Wiener's Laboratory, including the absorbed B serum for the segregation of subgroups $A_1$ and $A_2$. Determination of the $Rh_o$ factor was carried out with Wiener's anti-$Rh_o$ serum using the test tube technic recommended by this author. Tests to determine the presence or absence of blood group substance in saliva (Secretors and Non-secretors) were run in the following manner: Freshly collected saliva was inactivated by placing in boiling water for 10 minutes in order to destroy any enzymes present. One drop of heated saliva, in a dilution of 1 : 10, was mixed with one drop of properly diluted A or B serum containing 6 units of agglutinin. After standing for 15 minutes, 1 drop of a standard 2 per cent red cell suspension, A or B, was added to the saliva-serum mixtures. Controls with saline instead of saliva accompanied each test. The reactions were read macroscopically and microscopically after an interval of one hour at room temperature. Inhibition of specific agglutination was taken to indicate the presence of blood group substance in the sample of saliva, whereas the saliva was considered to be free from such substance when agglutination occurred specifically.

The results obtained in these various tests on poliomyelitis patients, together with the corresponding control material, are presented in tables 2, 3 and 4.

It will be seen from table 2 that the blood group distribution among the poliomyelitis patients differed in several respects from the normal control figures. Thus, there was a slightly lower incidence of blood group B (10.9

TABLE II

Blood Grouping in Poliomyelitis

| Series | Author | Locality | Year | Cases | Number | O % | A % | $A_1$ % | $A_2$ % | B % | AB % | $A_1B$ % | $A_2B$ % | Index $\frac{A_2+A_2B}{A_1+A_1B}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XI | Jungeblut, Karowe and Braham | Greater New York | 1944/45 | Poliomyelitis (paralytic) | 220 | 42.72 (94) | 43.18 (95) | 27.27 (60) | 15.90 (35) | 10.90 (24) | 3.18 (7) | 2.27 (5) | 0.90 (2) | 0.56 |
| | Jungeblut, Karowe and Braham | Greater New York | 1942–1945 | Normal | 20,211 | 45.49 (9195) | 36.41 (7350) | | | 13.60 (2749) | 4.49 (908) | | | |
| | Wiener | Greater New York | 1933–1943 | Normal | 1077 | 41.7 | 37.9 | 29.0 | 8.9 | 13.9 | 6.6 | 5.2 | 1.4 | 0.30 |

The figures given in parenthesis represent absolute numbers.

TABLE III

Distribution of $Rh_0$ Factor in Poliomyelitis Patients

| Cases | Number | $Rh_0$ positive | $Rh_0$ negative |
|---|---|---|---|
| Poliomyelitis (paralytic) | 187 | 81.3% (152) | 18.7% (35) |
| Normal | ~ | 85% | 15% |

TABLE IV

Secretion of Blood Group Substance in the Saliva of Poliomyelitis Patients

| Author | Cases | Locality | Number | Secretors | Non-secretors |
|---|---|---|---|---|---|
| Jungeblut, Karowe, Braham | Poliomyelitis (paralytic) | New York | | | |
| | A | | 87 | 73.56% (64) | 26.43% (23) |
| | $A_1$ | | 56 | 75% (42) | 25% (14) |
| | $A_2$ | | 31 | 71% (22) | 29% (29) |
| | B | | 23 | 65.21% (15) | 34.78% (8) |
| | AB | | 6 | 50% (3) | 50% (3) |
| | $A_1B$ | | 5 | 60% (3) | 40% (2) |
| | $A_2B$ | | 1 | 0% (0) | 100% (1) |
| | $A_1B$, AB | | 116 | 70.69% (82) | 29.3% (34) |
| Jungeblut, Karowe, Braham | Normal (A, B, AB) | New York | 111 | 81.98% (91) | 18.02% (20) |
| Schiff | Normal | New York | 74 | 82.4% | 17.6% |
| Wiener | Normal | New York | 130 | 82% | 18% |

per cent) among the paralytic patients as compared with the normal expectancy (13.6–13.9 per cent). In contrast to earlier observations, the figures for blood group O were somewhat lower while those for blood group A were slightly higher in the poliomyelitis patients than in the normal controls. Further examination, however, shows that the increase in blood group A (43.2 per cent against 36.4–37.9 per cent) was brought about essentially by a higher frequency of subgroup $A_2$. This is seen not only from the increase in the absolute frequency of $A_2$ (15.9 per cent against 8.9 per cent)

but also from the change in the relationship between $A_1$ and $A_2$ as expressed by the index $\frac{A_2 + A_2B}{A_1 + A_1B}$ (0.56 against 0.30). As far as the incidence of the $Rh_0$ factor is concerned, the data given in table 3 do not indicate any significant deviation from the normal figures. The frequency of "Secretors" and "Non-secretors," on the other hand, as shown in table 4, reveals again abnormal figures for the poliomyelitis patients in that the percentage of "Non-secretors" was appreciably elevated (29.3 per cent for poliomyelitis patients against 18 per cent for normal individuals).

To illustrate once more the difference in the blood group pattern of paralytic patients as contrasted with that found in normal individuals, we have brought together in table 5 the records of the two poliomyelitis series in New York of 1931 and 1944/45 with the corresponding normal local figures, supplemented by older and more recent records from normal populations in a number of larger cities from various parts of the United States.[17] Repetition of the characteristic features (slight elevation of O or A and slight decrease in B) in the blood group diagram of two poliomyelitis series, separated by over 10 years, is noteworthy as is the uniformity in the maintenance of normal distribution frequencies in several American urban centers over a similar and even longer period of time.

TABLE V

Blood Group Distribution in Two Poliomyelitis Series (New York) Compared with Blood Group Distribution in Eight Normal Series (New York, Boston, Detroit, Milwaukee)

| Author | Locality | Year | Cases | Number | O % | A % | B % | AB % |
|---|---|---|---|---|---|---|---|---|
| Jungeblut and Smith | Greater New York | 1931 | Paralytic Poliomyelitis | 236 | 46.6 | 38.1 | 10.6 | 4.7 |
| Jungeblut, Karowe and Braham | Greater New York | 1944/45 | Paralytic Poliomyelitis | 220 | 42.7 | 43.2 | 10.9 | 3.2 |
| Tiber | Greater New York | 1928 | Normal | 10,000 | 45.6 | 36.4 | 13.5 | 4.5 |
| Jungeblut and Smith | Greater New York | 1931 | Normal | 1,000 | 45.6 | 35.7 | 14.0 | 4.7 |
| Jungeblut, Karowe and Braham | Greater New York | 1942/45 | Normal | 20,211 | 45.5 | 36.4 | 13.6 | 4.5 |
| Wiener | Greater New York | 1933/43 | Normal | 1,077 | 41.7 | 37.9 | 13.9 | 6.6 |
| Jones | Boston | 1921 | Normal | 197 | 47.2 | 35.5 | 13.7 | 3.5 |
| Culpepper and Ableson | Detroit | 1921 | Normal | 5,000 | 44.4 | 36.0 | 14.2 | 5.1 |
| Seeger and Schaeffer | Milwaukee | 1930/33 | Normal | 489 | 42.1 | 36.2 | 13.9 | 7.8 |
| Graves | St. Louis | 1934 | Normal | 281 | 40.9 | 39.9 | 13.5 | 5.7 |

## DISCUSSION

The data reported in this paper tally with previously published figures in showing that individuals with blood group B occur "significantly" * less often among paralytic poliomyelitis patients than among comparable normal controls. The higher frequency of blood group A in our paralytic series,

* Whenever the term "significant" is used in the text it is meant to imply that the difference referred to is "statistically significant" as determined by the usual tests designed to exclude the influence of chance. It must be emphasized, however, that very small differences may attain statistical significance when based on a sufficient number of cases, although they may be of no particular "practical significance" in serving to explain certain phenomena.

We are greatly indebted to Dr. John W. Fertig and Miss Lillian Elvebach of the School of Public Health of the Faculty of Medicine, Columbia University, for their co-

however, is at variance with the bulk of the published material which shows a "significantly" higher percentage for blood group O. The apparent discrepancy may be partly resolved by the fact that the increase in blood group A in our poliomyelitis series is produced by a "significant" and selective elevation in the absolute and relative frequency of subgroup $A_2$, whereas the figures for subgroup $A_1$ remain unchanged. In this respect our observations are in complete harmony with those of Kleinschmidt.[11] The slight predominance of either blood group O or $A_2$, as the case may be, finds a simple and rational explanation if one accepts Thomsen's [18] theory that the so-called agglutinin $\alpha_2$ is really an agglutinin directed specifically against O red cells. Furthermore, the fact that $A_2$ individuals are preponderantly heterozygous—with the genotype $A_2O$ [19]—lends additional support not only to Thomsen's theory but may also provide an understanding for the apparently more frequent association of the phenotypes O and $A_2$ with the group of paralytic patients. A new finding which has emerged from this work and which will require further investigation before it can be generally accepted is our observation that the percentage of the "Non-secretor" type in paralytic poliomyelitis was "significantly" above the figures considered normal at the present time. Since the inability to secrete blood group substance peripherally represents a minority (or deficiency) trait among normal individuals, considerable interest attaches to its seemingly increased occurrence in patients of a disease as selective as poliomyelitis.

In conclusion it may be said that paralytic poliomyelitis selects individuals with blood groups O or $A_2$ and "Non-secretor" types somewhat *more* frequently and, vice versa, individuals with blood group B and "Secretor" types somewhat *less* frequently than these groups occur in the normal populations. This fact does not, by itself, bring the problem of predisposition to the disease any nearer to a practical solution. If it is true that both endogenous and exogenous factors operate in conjunction to precipitate the paralytic attack, consideration of endogenous dissimilarities alone cannot possibly measure more than a fraction of the components that condition the state of physiological equilibrium. Hence, the resulting indices of resistance or susceptibility, at best, are only relative and far from absolute. More important yet, since

operation in scrutinizing our data as to their statistical significance. Their conclusions may be summarized briefly as follows:

1. None of the individual paralytic poliomyelitis series shows a statistically significant difference in the frequency of occurrence of any single blood group as compared with the corresponding control series. However, taking into consideration all of the series of paralytic cases against their corresponding controls, in view of the consistency of the difference, there may be said to be a statistically significant decrease of Blood Group B and an increase of O as compared to the controls. It must be emphasized, however, that the small differences attain significance only because of their consistency and because of the very large numbers in some of the groups.

2. The $A_1/A_2$ ratio of the two paralytic poliomyelitis series (Kleinschmidt; Jungeblut, Karowe, and Braham) differs significantly from the corresponding normal control figures.

3. The increase of "Non-secretors" in the paralytic poliomyelitis series is significant when compared with the normal figures.

4. The probability of obtaining the difference in question by chance alone is, in each case, less than one in a hundred.

the investigation of blood groups is limited to phenotypes, no information is gained on the genetic mechanisms involved in the genotype of the individual. However, our data serve to emphasize again the importance of hereditary influences as the major determinants for the crippling caused by the disease. This viewpoint has been repeatedly discussed by competent observers. Evidence for the existence of an autosomal recessive gene for susceptibility to paralytic involvement was recently adduced by Addair and Snyder.[20] Why the genetic transmission of such factor or factors should be associated with a given group gene and not with another is a question that cannot be discussed at present without the risk of hazardous speculation. Further studies on blood grouping in families in which multiple cases of poliomyelitis have occurred, with closer examination of the respective pedigrees, would probably throw more light on this problem.

## Summary and Conclusions

1. A survey of the literature on blood grouping in poliomyelitis shows essential agreement that the incidence of blood group B is slightly decreased and that of blood group O slightly increased in paralytic patients as compared with corresponding normal control populations.

2. Blood group determinations on a series of 220 paralytic poliomyelitis patients from Greater New York during 1944/45 confirmed the shortage of blood group B but indicated a slight increase of blood group A over the normal control figures. This increased percentage of blood group A was caused selectively by elevation of the absolute and relative frequency of subgroup $A_2$, whereas the figures for subgroup $A_1$ remained essentially unchanged.

3. The fact that in the present study blood group $A_2$ predominated among the poliomyelitis patients whereas in most other studies blood group O was in excess, may be explained on the basis of Thomsen's theory that the so-called agglutinin $\alpha_2$ is specifically directed against O cells.

4. The poliomyelitis series showed a distribution of the $Rh_0$ factor which differed very little from the normal value.

5. The series of poliomyelitis patients showed an increased occurrence of the "Non-secretor" type against normal control figures.

6. The available data suggest that individuals with blood groups O, $A_2$ and "Non-secretor" types tend to suffer paralytic involvement in poliomyelitis more often than one would expect from the normal distribution figures for these groups; vice versa, individuals with blood groups B and "Secretor" types seem to be somewhat less frequently thus affected as compared with the distribution of these groups in normal populations. The frequency of occurrence of blood group $A_1$ in paralytic patients appears to be essentially the same as found in normal controls.

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# RIGHT VENTRICULAR AND RIGHT AURICULAR HYPERTROPHY OF OBSCURE ORIGIN *

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In every collection of a large number of patients with heart disease there are a few examples of cardiac enlargement and cardiac failure in which there are no clues to the nature of the underlying pathologic process. White [1] has stated that about one such case is encountered yearly at the Massachusetts General Hospital. Three were reported from that hospital in 1942.[2] Ordinarily when a patient with heart disease of obscure origin is encountered an attempt is made to fit him into one of the well recognized etiologic categories of heart disease, but there is a large group of poorly recognized disorders of the heart and aorta which merits our attention and into which many of these confusing cases may fall.[3] The majority of patients with so-called idiopathic cardiac hypertrophy have shown enlargement of the left ventricle alone or diffuse cardiac enlargement. Two cases of cardiac hypertrophy and congestive failure of uncertain etiology which exhibited unusual features have recently been observed in this clinic. One patient proved to have hypertrophy confined to the right side of the heart associated with dilatation of the pulmonary arterial tree; the other displayed enlargement and dilatation of the right auricle and moderate hypertrophy of the left ventricle.

## Case Reports

*Case 1.* J. P., a 14-year-old schoolgirl, was first seen in the clinic on August 21, 1944. She complained of repeated hemoptyses. In May 1944, she filled a handkerchief with bright, red blood. The following morning she coughed up a small dark clot of blood. Two other small hemorrhages occurred in the month prior to the examination.

When she was an infant the family physician said her heart was "weak." On two occasions the question of some cardiac abnormality was raised during physical examinations at school. For one year she had experienced dyspnea and dizziness when walking up an incline or running. When she played baseball, she had developed the practice of having one of her playmates run the bases for her. Cyanosis had not been noted at birth nor subsequently. There was no other history of cardiac symptoms and no rheumatic manifestations had been noted. The past history and family history were not significant in other respects.

*Physical Examination:* The patient was a well-developed girl who appeared to be in good health. There was some fullness in the region of the thyroid gland but no abnormal pulsations nor dilated vessels were present in the neck. The lungs were clear. The left precordial area displayed a diffuse systolic heaving which was particularly prominent in the second and third intercostal spaces. The heart was slightly enlarged. Along the left sternal margin in the region of the systolic pulsation there

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was a moderately loud, blowing, systolic murmur and a conspicuously accentuated pulmonic second sound. In the same area there was a brief, faint, early diastolic sound. The systolic murmur was transmitted toward the apex. The blood pressure was 118 mm. Hg systolic and 92 mm. diastolic. There was no cyanosis or clubbing of the fingers or toes. The remainder of the examination was negative.

*Laboratory Data:* The hemoglobin was 16.6 gm. (106 per cent). The blood Kahn reaction was negative. Fluoroscopic examination of the heart disclosed hypoplasia of the aorta and dilatation of the undivided portion of the pulmonary artery. The

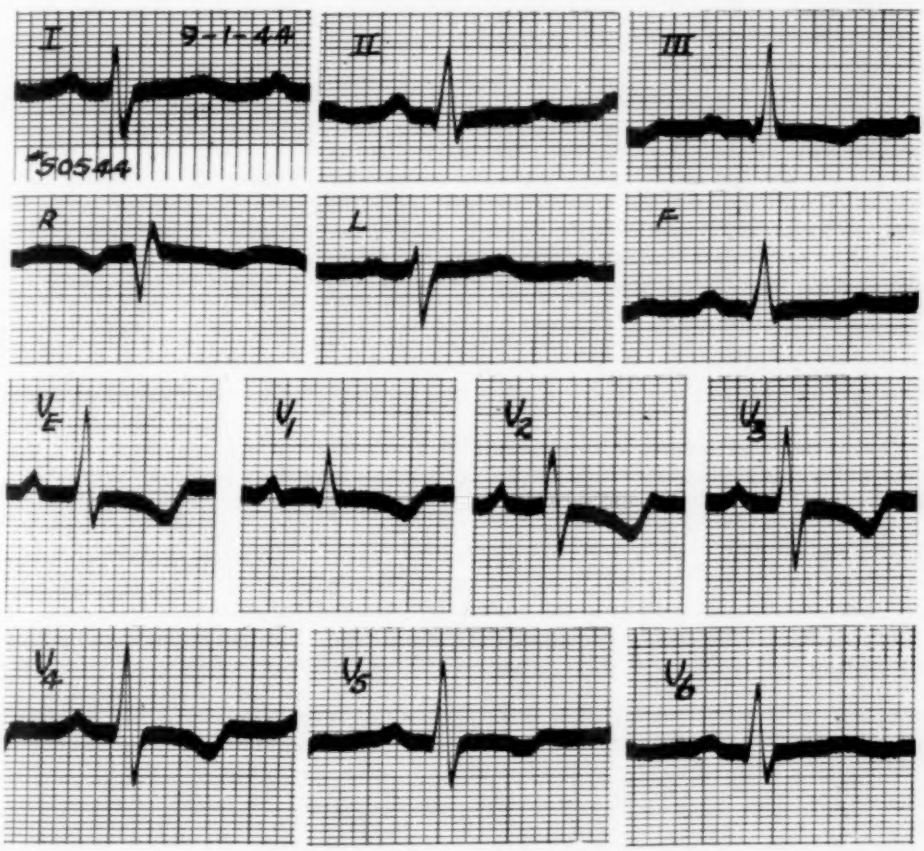


FIG. 1. *Case 1.* September 1, 1944. Standard leads show slight right axis deviation. The precordial leads display prominent, late R-waves in Leads $V_1$ and $V_E$, and inverted T-waves in all leads except $V_6$. These changes suggest moderate right ventricular hypertrophy.

retrocardiac space was clear throughout. The frontal plane area of the cardiac silhouette was 29 per cent above the predicted normal by both orthodiagraphic and teleoroentgenographic methods. The standard and unipolar electrocardiograms display slight right axis deviation and rather broad, notched P-waves in all leads (figure 1). The precordial leads exhibit prominent, late R-waves and absent S deflections in lead $V_1$ and inverted T-waves in all of the records except lead $V_6$. These findings are suggestive of moderate right ventricular hypertrophy.

*Subsequent Course and Second Admission:* The patient was not seen again until October 11, 1944 when she was admitted in extremis. One week earlier minimal

generalized edema, and pain in the abdomen, back and right shoulder had appeared. For two or three nights she had been restless and unable to sleep well. She continued to attend school until the day prior to admission when she developed severe dyspnea. Soon thereafter the edema of the ankles and face became more pronounced.

*Physical Examination:* The patient was orthopneic and very cyanotic. There was moderate edema of the lower extremities and face. The heart rate was 120 per minute and a gallop rhythm was heard. Auscultation was unsatisfactory but a loud, harsh systolic murmur was thought to be present over the entire precordium. The patient died 20 minutes after admission.

*Postmortem Examination* (Performed by Dr. Martin R. Sutler, Jr.): The heart appeared to be in an abnormal position when inspected in situ. No part of the left ventricle could be seen; the anterior aspect consisted of the right atrium and right ventricle. The heart weighed 344 gm. (average normal at this age is 157.4 gm.[4]). The right ventricular wall was 7 mm. in thickness; the left ventricular wall was 8 mm. in thickness. The right atrium was moderately dilated. The leaflets of all valves were normal and the interatrial and interventricular septa were intact. The circumferences of the valves were: mitral, 80 mm.; tricuspid, 112 mm.; aortic, 55 mm.; pulmonic, 75 mm. The coronary arteries were normal. The main pulmonary artery was a little greater in circumference than normal. The pulmonary arteries throughout, down to the smallest branch, appeared to be dilated. There was an early infarction of the lower two-thirds of the left lower lobe apparently resulting from a rider's embolus extending into the main arterial branch to the lower lobe and straddling into a small radicle from this branch. There were no abnormalities of the thoracic aorta and the ductus arteriosus was obliterated. There was moderate ascites and slight pleural and pericardial effusion.

Microscopic examination of the heart disclosed muscle fibers in a patchy distribution which appeared somewhat larger than normal. There were petechial hemorrhages in the sub-epicardial fat and non-lipoidal vacuolar changes in the subendocardium. The aorta exhibited marked hypoplasia. The lungs displayed an intense, acute exacerbation of chronic passive congestion, hemorrhage into alveolar spaces and severe catarrhal bronchitis. There was chronic passive congestion of the liver and spleen.

*Case 2.* H. C., a 21-year-old bookkeeper, entered the University Hospital on June 14, 1944, complaining of dyspnea and ankle edema. She had been aware of some dyspnea on exertion all her life. An episode of ankle edema lasting two or three days occurred in December 1943. In January 1944, she had fever and a productive cough for three or four days. Ankle edema reappeared in April 1944, and ascites developed soon thereafter. Early in May 1944, she was in hospital for four weeks and was considerably relieved by digitalis and diuretics. Roentgenographic examination was said to have revealed cardiac enlargement and earlier films made in 1937 were found to display similar changes in the heart. One week prior to admission her symptoms recurred despite continued bed rest. Her diet had been adequate. She had minimal tuberculosis at age 13 which required treatment in a sanatorium for seven months. The past history and family history were not significant in other respects.

*Physical Examination:* The patient was normally developed and in a good state of nutrition. She was severely dyspneic and moderately cyanotic. There was a persistent slightly productive cough. There were occasional unusually prominent, systolic venous pulsations in the neck; these were found to correspond to periods of atrio-ventricular nodal rhythm. The heart was very much enlarged and a forceful apex impulse was located in the mid-axillary line at the fifth interspace. The cardiac sounds were loud and the pulmonic second sound was conspicuously accentuated. No significant murmurs were heard. The blood pressure was 124 mm. Hg systolic and 80 diastolic. Numerous râles were present over the lower portions of both posterior lung fields. A smooth, firm, tender liver extended to the level of the right iliac crest and

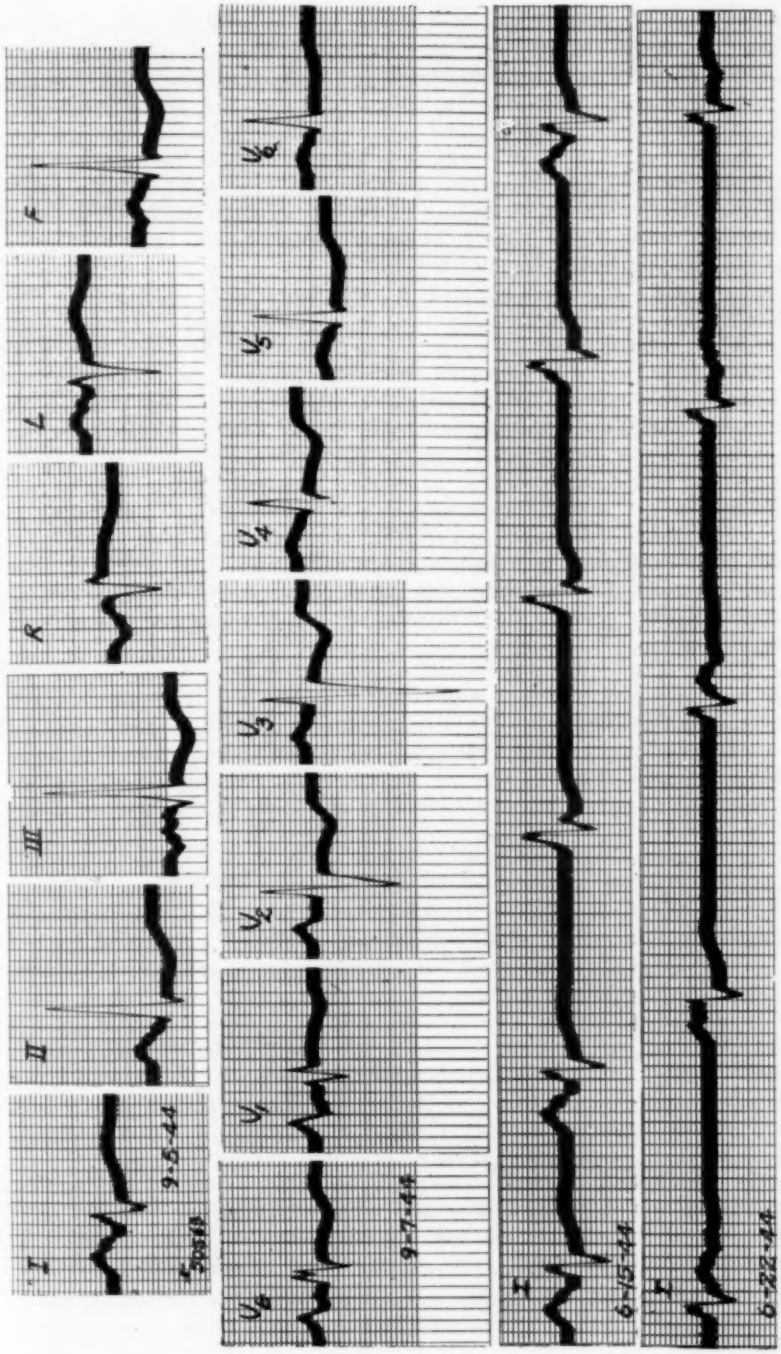


FIG. 2. *Case 2.* Standard leads on September 5, 1944, show slight right axis deviation and unusually broad, notched P-waves. Precordial leads on September 9 display prominent R′ deflections in Lead $V_1$. Electrocardiograms suggest auricular hypertrophy and incomplete right bundle branch block. Inverted T-waves in Leads II, III, and precordial leads are probably due in part to digitalis. Records on June 15 and 22 show transient atrio-ventricular nodal rhythm.

displayed questionable pulsation. There was moderate edema of the legs and the sacral region.

*Laboratory Data:* Albuminuria of slight degree was found from time to time but the urine was not otherwise abnormal. The hemoglobin ranged from 92 per cent to 115 per cent and there was a moderate leukocytosis (14,600) on admission; the blood was normal in other respects. Examinations of the sputum, stool, serum proteins and blood chlorides and cultures of the blood and sputum were negative. The blood Kahn reaction was negative. Several roentgenographic examinations of the thorax revealed considerable cardiac enlargement, broadening of the waist of the heart, flattening of the cardiophrenic angle bilaterally, and reduction of the retrocardiac space. Fluoroscopic observation disclosed no pulsations along the lower borders of the heart and marked diminution of the pulsations of the upper borders.

Electrocardiograms: The standard and unipolar limb leads on June 15, 1944, showed moderate right axis deviation with very broad, large, notched P-waves in all leads and unusually large R-waves in Leads II and III. The T-waves were flat in Lead I and inverted in Leads II and III; this was attributed, at least in part, to digitalis. Transient atrio-ventricular rhythm was also present. Similar electrocardiograms were recorded on June 16 and 26, September 5, and October 4. Records taken on June 22 displayed a transient low atrio-ventricular rhythm with marked variations in the location of the pacemaker, and occasional probably reëntrant beats. Precordial leads taken on September 7 exhibit prominent late R′ deflections and unusually large P-waves in Lead $V_1$, notched R-waves in Lead $V_E$, inverted T-waves in all leads, and unusually large QRS deflections, particularly in Leads $V_2$ and $V_3$ (figure 2). These records suggest auricular and ventricular hypertrophy and probable incomplete right bundle branch block but they are not characteristic of preponderant right or left ventricular hypertrophy.

*Hospital Course:* The patient was treated for congestive heart failure in the usual fashion. She was in an oxygen tent continuously for the first two months in the hospital. Her course was complicated by a transient left facial paralysis on June 18, and bronchopneumonia on June 22. She made slow, gradual improvement and in September she was permitted out of bed for short periods. Shortly thereafter manifestations of congestive heart failure reappeared, grew rapidly worse, and she died on October 7, 1944.

*Postmortem Examination* (Performed by Dr. Martin R. Sutler, Jr.): The heart weighed 432.5 gm. The left ventricular wall was 15 mm. thick and appeared hypertrophied. The right ventricular wall measured 4 mm. in thickness. The right atrium was greatly enlarged and dilated. The left atrium displayed a calcified, sclerotic plaque 3 by 2 cm. in size in the endocardial and subendocardial tissue of its left posterolateral wall. The coronary sinus opening into the right atrium appeared very large at its mouth and dilated throughout its course. All the valves were normal and their circumferences were: mitral, 110 mm.; tricuspid, 126 mm.; aortic, 54 mm.; and pulmonic, 60 mm. None of the common congenital cardiovascular anomalies were present. There was acute exacerbation of chronic passive congestion of the lungs. The pulmonary vessels appeared normal. There was chronic passive congestion of the liver and spleen and a small effusion in each pleural space.

Microscopic examination disclosed moderate hypertrophy of the myocardium with an increase in stroma and an anomalous pattern with interlacing of the heart muscle fibers, especially in the left ventricle. The coronary arteries were negative. The pulmonary arterial and arteriolar walls were not thickened. Congestion of all viscera was present.

## Comment

As our knowledge increases more and more, cases now classified as idiopathic cardiac hypertrophy will no doubt be placed in definite etiological

categories. The development of the sphygmomanometer made possible the separation of cases of hypertensive heart disease from the idiopathic group and the recognition of abnormal glycogen storage permitted the identification of cases of von Gierke's disease. It is desirable that each example of cardiac enlargement of uncertain origin be carefully investigated in the hope that some clue to the nature of the pathological process be uncovered. In the majority of the reported cases of cardiac hypertrophy of obscure etiology the patients have been infants or children. In 1942, Weisman[5] found 70 cases of this disorder in children in a survey of the literature which included the earlier reviews of Kugel and Stoloff[4] and Mahon.[6] In this large series, 70 per cent of the patients were under one year and none were over nine years of age. Reports of idiopathic cardiac hypertrophy in adults have, for the most part, concerned isolated examples, but Levy and Von Glahn[7] reviewed 14 cases from the literature and reported 10 of their own. Kaplan, Clark, and de la Chapelle[8] were able to find 11 cases at the Bellevue Hospital during a three year period. The criteria which have led different writers to consider cases of cardiac hypertrophy as idiopathic or unclassifiable, on an etiologic basis, have varied considerably. The reason for this is that there are still differences of opinion as to just what structural lesions disclosed by postmortem examination can be regarded as adequately accounting for this change in the heart muscle. In some of the reported instances the observations made have not been sufficiently extensive to exclude all the known causes of cardiac hypertrophy.

The two cases which form the basis of this report showed involvement of the right heart, particularly, and the predominant symptoms were those of right-sided cardiac failure. The incidence of cor pulmonale and its numerous underlying causes have been discussed in the publications of Griggs, et al.,[9] Scott and Garvin,[10] and von Bonsdorff.[11] It is necessary here only to point out that our patients showed no evidence of primary pulmonary disease or distortion of the thoracic cage[12, 13] which could account for the cardiac involvement. These two patients presented many symptoms and signs suggestive of pulmonary disease with pulmonary arterial hypertension, particularly cough, dyspnea, cyanosis, hemoptysis, systolic pulsation along the upper left sternal margin, an accentuated pulmonic second sound, and electrocardiographic signs suggestive of right ventricular hypertrophy. The various etiologic factors which may be responsible for this disorder have been reviewed by Brenner[14] and Balboni[15] and subdivided by the latter into primary pulmonary arteriosclerosis (obliterating endarteritis of small arterioles) and secondary pulmonary arteriosclerosis (atherosclerosis of large arteries resulting from conditions producing an elevated arterial pressure in the pulmonary arteries). Our first case revealed only dilatation of all the pulmonary arteries rather than narrowing of the lumina or thickening of the arterial walls with associated dilatation of the type described by Brenner.[14] Our second case exhibited no abnormalities of the pulmonary arteries.

Idiopathic hypertrophy of the right heart has been described only rarely.

A survey of the literature has been made and we have considered the hypertrophy idiopathic only when: (a) the clinical, pathological, and microscopic examinations were adequate to exclude all known causes of right ventricular hypertrophy; (b) the examination of the heart at autopsy confirmed the diagnosis of this cardiac abnormality; and (c) there were no congenital cardiovascular anomalies other than the right heart hypertrophy itself. We were able to find six reported cases which met these criteria and are considered as acceptable (table 1). The two cases described in this report are added to this group, although it must be pointed out that in Case 2, the involvement was most striking in the right auricle and that some hypertrophy of the left ventricle was also present. In addition, we have found six reported cases which are considered as probably acceptable (table 2). The authors who published these were of the opinion that the minor pathological changes in the lungs were inadequate to account for the cardiac enlargement. Two of the patients showed minor pulmonary arteriolar narrowing; one exhibited sclerotic changes in the larger pulmonary arteries; one had purulent bronchitis and bronchiectasis; another displayed emphysema; a microscopic examination of the lungs was not made in the case of the sixth patient in this group. The cases reported by Hueter [23] and Zuber [24] have been included as examples of right ventricular hypertrophy of unknown origin in other studies of this subject; they are not included as such in this review because a patent ductus arteriosus was present in each of them and in one the foramen ovale was open [23] in addition.

All of the reports have not been sufficiently detailed to make possible an extensive analysis of the symptoms manifested by the various patients, but a study of tables 1 and 2 will give information which may have value in the clinical consideration of possible examples of idiopathic right cardiac hypertrophy. There were four males and 10 females. The age range was 10 months to 73 years. Dyspnea, appearing initially on exertion but later at rest, cyanosis, cough, ascites and edema were the most common, important complaints. Congestive failure in these patients was of the type generally classified as right-sided heart failure; ascites, edema, and hepatic and venous engorgement predominated over the signs of respiratory embarrassment. In some patients, when heart failure occurred, it progressed to a fatal termination in a few days; other patients survived for several months or years despite repeated episodes of decompensation. The most frequent and most significant abnormal physical signs were a systolic murmur and a prominent systolic pulsation in the pulmonic area, and an accentuated, often palpable, second sound in the same zone. These signs were particularly striking in our Case 1. Clubbing of the fingers and toes and polycythemia occurred infrequently and were not as striking as in most patients with cyanotic congenital heart disease. The death of 12 of the 14 patients was due to cardiac failure; of the two remaining patients one died of bronchopneumonia and the other of suppurative pylephlebitis. Roentgenographic observations usually disclosed signs of right ventricular hypertrophy, dilatation of the pul-

TABLE I

Acceptable Cases

| No. | Author | Sex | Age | Clinical Features | Pathology | Electrocardiograms |
|---|---|---|---|---|---|---|
| 1 | Howland [16] | F | 2½ | Pain in heart, syncope, cyanosis, and anorexia. | Heart weighed 120 gm. R.V. wall 6.6 mm.; L.V. wall 6.0 mm. Hypertrophy and dilatation of right heart. Pulmonary artery dilated. Walls of pulmonary vessels thin and delicate. | None reported. |
| 2 | Oppenheimer [17] | M | 46 | Cough, dyspnea, accentuated pulmonic second sound. Death due to suppurative pylephlebitis. | Hypertrophied right ventricle; small left ventricle. Huge pulmonary artery and main branches with dilatation almost to pleural surface. Some arteriosclerotic plaques. Slight intimal thickening of arterioles. | Right axis deviation; inverted $T_3$ and $T_4$. |
| 3 | Oppenheimer [17] | F | 60 | Cyanosis, dyspnea, moderate polycythemia. Died of acute congestive heart failure of three days' duration. | Marked right ventricular hypertrophy; small left ventricle and rather small aorta. Huge dilatation of pulmonary artery and dilatation of all the pulmonary arteries. | Right axis deviation; inverted $T_3$ and $T_4$. |
| 4 | De Navasquez, et al.[18] | M | 30 | Attacks of syncope, cough, insomnia, cyanosis, and slight dyspnea for 1 year. | Heart weighed 530 gm. L/R ratio 0.87. Dilatation of pulmonary artery throughout its branches as far as periphery of lung. Fatty atheroma in streaks and plaques and irregular thickening of intima in larger branches, questionable medial hypertrophy in smaller branches. | Right axis deviation with inversion of $T_3$ and $T_4$; depression of RS-T segment. |

TABLE I—*Continued*

| No. | Author | Sex | Age | Clinical Features | Pathology | Electrocardiograms |
|---|---|---|---|---|---|---|
| 5 | De Navasquez, et al.[18] | M | 49 | Dyspnea, clubbing, cyanosis, and polycythemia for 3 or 4 years. | Heart weighed 630 gm. L/R ratio 0.80. Pulmonary artery uniformly dilated as far as first division. Second branches conspicuous and show patchy fatty atheroma. Remaining branches normal. | Marked right axis deviation with low voltage and flattening of $T_2$. |
| 6 | East [19] | F | 24 | Attacks of right ventricular failure for 6 years. Systolic pulsation and very loud second sound in pulmonic area. | Heart weighed 391 gm. Right ventricle—210 gm. Right auricle much distended. Catarrhal cells in pulmonary alveoli, slight hypertrophy of arteriolar muscle coats. No change in intima. | None reported. |
| 7 | Rosenbaum | F | 14 | Hemoptysis and dyspnea on exertion for 5 months. Rapid, terminal congestive heart failure. Systolic pulsation and murmur, palpable accentuated second sound in pulmonic area. | Heart weighed 344 gm. Marked right ventricular hypertrophy and right auricular dilatation. Dilatation of pulmonary artery and all its branches. Pulmonary arterioles normal. Aorta hypoplastic. | Slight right axis deviation, broad P waves in all leads. Precordial leads suggestive of right ventricular hypertrophy. |
| 8 | Rosenbaum | F | 21 | Dyspnea on exertion all her life. Progressive ankle edema, ascites, cyanosis and congestive heart failure for 11 mos. Accentuated pulmonic second sound. Slight polycythemia. | Heart weighed 432.5 gm. Tremendous enlargement and dilatation of right atrium. Moderate left ventricular hypertrophy. Pulmonary vessels normal. | Moderate right axis deviation with broad P waves in all leads and inverted $T_2$ and $T_3$. Chest leads suggest incomplete right bundle branch block. |

monary arteries and unusual prominence of the right ventricular conus. The electrocardiograms uniformly displayed right axis deviation. The precordial electrocardiograms in our Case 1 confirmed the diagnosis of right ventricular hypertrophy. In Case 2, the electrocardiograms suggested auricular hypertrophy and incomplete right bundle branch block, but were not characteristic of either right or left ventricular hypertrophy; transient atrio-ventricular nodal rhythm also occurred in this instance.

Dilatation of the pulmonary arteries was described in all but two of the 8 cases listed in table 1 and in four of the six cases in table 2. As in Case 1, in many instances this dilatation extended to the very periphery of the lungs. Congenital widening or aneurysmal dilatation of the main stem of the pulmonary artery or its branches as a primary condition is quite rare. Costa [25] reviewed the literature on this subject extensively and found that pulmonary arterial aneurysms were associated with other congenital cardiovascular anomalies in 47 per cent of the cases; luetic arteritis (about 20 per cent), mycotic-embolic arteritis (6 per cent), rheumatic heart disease, pulmonary disease of various types, phlebitis of the pulmonary veins, or trauma accounted for nearly all of the other examples of this disorder. Costa felt that this was unexpected in view of an earlier study in which he had discovered an anomalous hypoplastic histological structure in the pulmonary arterial walls in 14 per cent of 210 cases.[26] Clarke, et al.,[20] Abbott,[27] D'Aunoy and von Hamm,[28] and Scott [29] have all been similarly impressed by the infrequency of primary pulmonary arterial dilatation. It is noteworthy that in Costa's group of 73 cases of pulmonary arterial aneurysm, 71 per cent displayed hypertrophy confined to the right ventricle and about 35 per cent exhibited dilatation of the ramifications of the pulmonary arterial system.[25]

The relationship between dilatation of the pulmonary arteries and right cardiac hypertrophy such as was present in our Case 1 and such as was observed in the similar cases listed in tables 1 and 2 is not clear. Right ventricular enlargement has been a common finding in the recent reports of pulmonary aneurysm.[28, 29, 30] Inasmuch as aortic aneurysms uncomplicated by aortic valvular disease are rarely responsible for left ventricular hypertrophy, it would be surprising if pulmonary aneurysms should, of themselves, give rise to right ventricular hypertrophy. The factor of relative pulmonic insufficiency may be operative in patients with more diffuse pulmonary arterial widening; the presence of pulmonary diastolic murmurs in some cases suggests that this is the case.[17] Brenner [14] has expressed the opinion that in primary pulmonary arteriosclerosis "the vascular lesions are rarely extensive enough in themselves to embarrass the pulmonary circulation seriously and more probably they and the hypertrophy of the right side of the heart are manifestations of some common unknown cause." Here, too, it may well be that the right cardiac enlargement and the pulmonary arterial dilatation are related only insofar as they have a common etiological background.

TABLE II

Probably Acceptable Cases

| No. | Author | Sex | Age | Clinical Features | Pathology | Electrocardiograms |
|---|---|---|---|---|---|---|
| 1 | Clarke, et al.[20] | F | 10 mos. | Numerous attacks of dyspnea and cyanosis. Progressive severe cough. Died from bronchopneumonia. | Dilatation and hypertrophy of right ventricle. Pulmonary artery dilated above valve and throughout its branches. Vessel walls normal. Purulent bronchitis, bronchiectasis with peribronchial fibrosis. | None reported. |
| 2 | Ulrich [21] | F | 27 | Weakness on exertion for 12 years. Hoarseness and hemoptysis for 3 years. Dyspnea, edema, cyanosis, uterine bleeding, and slight polycythemia. Mitral murmur. | Heart weighed 360 gm. Great dilatation and moderate hypertrophy of right auricle and right ventricle. Pulmonary artery dilated. Sclerotic thickening of larger branches of pulmonary artery and dilatation of some of the middlesized branches. No sclerosis of arterioles. | Right ventricular preponderance. |
| 3 | De Navasquez, et al.[18] | M | 55 | Dyspnea, cough, ascites, and edema. Repeated attacks of short duration. | Heart weighed 650 gm. L/R ratio 0.84. Great hypertrophy of right ventricle; other chambers normal. Pulmonary artery showed dilatation and slight atheroma in streaks in main branch. Pulmonary arteries 2 to 10 mm. in size showed crescentic thickening of intima. Other vessels normal. | None reported. |

TABLE II—*Continued*

| No. | Author | Sex | Age | Clinical Features | Pathology | Electrocardiograms |
|---|---|---|---|---|---|---|
| 4 | East [19] | F | 31 | Dyspnea and cyanosis for years. Ascites, edema and venous engorgement prior to death. Systolic murmur and pulsation, accentuated and palpable second sound in pulmonic area. | Heart weighed 415 gm. Right ventricle greatly enlarged, wall 5 mm. thick; left ventricle normal, wall 7 mm. thick. Pulmonary artery large and prominent. No macroscopic abnormality of pulmonary vessels; no sections reported. | Right axis deviation with diphasic $T_2$ and inverted $T_3$. |
| 5 | East [19] | F | 31 | Increasing dyspnea, venous engorgement, cyanosis, edema, and right heart failure. Systolic pulsation and accentuated, palpable second sound in pulmonic area. | Heart weighed 372 gm. Massive hypertrophy of right ventricle; left ventricle normal. Right auricle engorged. Pulmonary artery large. Muscle coats of smaller arterioles slightly thickened and a few smallest arterioles obliterated. | Right axis deviation with inverted $T_3$. |
| 6 | Armstrong [22] | F | 73 | Dyspnea, ascites, ankle edema, and cyanosis for 4 years. Died suddenly. Systolic murmur and accentuated second sound in pulmonic area. | Heart weighed 425 gm. Great hypertrophy of right ventricle and auricle. Severe atheroma in pulmonary arteries. Pulmonary arterioles normal. Emphysematous bullae and fine, even pulmonary emphysema. | Right ventricular preponderance. |

TABLE III

Etiological Hypotheses for Idiopathic Cardiac Hypertrophy *

A. Congenital Imperfections or Anomalies of the Cardiovascular or Pulmonary Arterial Systems.
   1. Congenital narrowing of the capillary bed (Emerson [31]).
   2. Unrecognized arterio-venous aneurysm (Powers, et al.[32]).
   3. Congenital narrowing of excessive size of aorta (Fraentzel [33]).
   4. Anomalies of the coronary arteries (Abrikossoff,[34] Carrington and Krumbhaar [35]).
   5. Underdevelopment of the coronary arteries with chronic myocardial ischemia (Weiss [3]).
   6. Congenital medial sclerosis of the coronary arteries (Kissane and Fidler [36]).
   7. Imperfection of the stuff of the pulmonary artery (Schwalbe,[37] Clarke, et al.[20] or loss of elastic tissue of the pulmonary artery with overload of the heart (Ulrich [21]).
   8. Excessive resistance in the pulmonary system (Fraentzel [33]).
   9. Disorders of the cardiac nervous system (Fraentzel [33]).
   10. Constitutional basis, particularly hypertension in the parents (Katz,[38] Mussliner [39]).
   11. Inherited tendency to cardiac anomalies (Sprague, et al.,[40] Clarke, et al.[20]).

B. Abnormal Infiltrations of the Heart.
   1. Non-suppurative myocardial infiltration with dilatation and hypertrophy (Kugel and Stoloff,[4] Kugel [41]).
   2. End stages of glycogenesis (Antopol, et al.[42]) or cardiomegalia glycogenica circumscripta (Van Creveld and Van der Linde [43]).
   3. Diffuse rhabdomyoma (Virchow [44]).
   4. Fatty heart (Fraentzel [33]).
   5. Round cell infiltration causing fatty degeneration and atrophy (Riesenfeld [45]).
   6. Endocardial fibrosis (Mahon,[6] Weisman [5]).
   7. Synechia of the pericardium (Michaud [46]).

C. Infections.
   1. Respiratory infections of the mother during pregnancy (Weiss [3]).
   2. Respiratory infections of the new-borne (Weiss [3]).
   3. Recurrent myocarditis (Krstulovic,[47] White [26]).
   4. Effects of pertussis with prolonged coughing (Hauser [48]).
   5. Diphtheritic myocarditis (Fraentzel [33]).
   6. Toxic myocarditis associated with various infections (Fahr and Kuhle,[49] Ceelen [50]).

D. Metabolic Disorders.
   1. Obesity (Hamman [51]).
   2. Avitaminosis (Kugel and Stoloff [4]).
   3. Glycogen storage disease (von Gierke,[52] van Creveld [53]).
   4. Excessive alcohol consumption (Michaud,[46] Fraentzel,[33] Blumer [54]).
   5. Hypothyroidism.
   6. Unknown metabolic disorders (Powers, et al.[32]).

E. Diseases of Other Organs or Systems.
   1. Disease of the kidney (Fraentzel [33]); scarlatinal nephritis (Michaud [46]).
   2. Anemia of long duration (Michaud [46]).
   3. Hypersecretion (Hedinger [55]) or hyposecretion (Michaud [46]) of chromaffin tissue.
   4. Status thymicolymphaticus (Henoch,[56] Riesenfeld,[45] Steiner and Bogin [57]).

F. Transient Overloading of the Heart with Dilatation and Subsequent Hypertrophy (Eyster,[58] Powers, et al.[32]).
   1. Antecedent hypertension (Kaplan, et al.[8]).
   2. Allergy (Mahon [6]).
   3. Intrauterine circulatory disturbance present only in fetal life disappearing or becoming unrecognizable at birth (Howland,[16] Simmonds [59]).
   4. Intrauterine fibrosis of lungs with narrowing of capillary field, increasing pulmonary arterial pressure during the first few hours of life (Clarke [20]).
   5. Enlargement of the heart in pregnancy (Fraentzel,[33] Sodeman [60]).

* Authors cited mention or support the theory in question but are not necessarily the original proponents of that particular hypothesis.

The majority of the hypotheses which have been advanced to account for cardiac hypertrophy of obscure origin have been summarized in table 3. It is outside the scope of this report to discuss the relative merits of these various theories. In individual cases thorough pathological study will exclude many of these postulated factors, particularly those in the group of abnormal myocardial infiltrations. The two patients reported here may be considered examples in which such an exclusion is possible. In other instances, the underlying difficulty may be disclosed by careful investigation of the patient's history or special clinical examinations may be developed in the future which will prove useful in this regard. Such observations are impossible in those cases in which congestive failure appears and terminates fatally in a very short time. One of the explanations of obscure cardiac hypertrophy which seems most plausible is that of overloading of the heart with transient dilatation and subsequent hypertrophy such as Eyster [58] produced in experimental animals. It is conceivable that obscure infections occurring in utero or in infancy may make the heart more susceptible to such transient overloading.

## Summary

Two cases of idiopathic cardiac hypertrophy occurring in young women and terminating fatally with congestive heart failure are described. In one patient the hypertrophy was confined to the right ventricle and auricle and was accompanied by dilatation of the entire pulmonary arterial tree. In the second case the most striking enlargement was found in the right auricle and was associated with moderate left ventricular hypertrophy. The pulmonary vessels were entirely normal in this patient. Careful clinical observations employing new technics such as right heart catheterization may furnish information which will be of importance in solving the problem of the obscure etiology of such cardiac abnormalities.

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# HUMAN GLANDERS: REPORT OF SIX CASES *

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GLANDERS, primarily an equine disease, occurs naturally in two forms, namely acute or chronic systemic glanders, and cutaneous glanders. In the past, the disease in man has usually been contracted by direct or indirect contact with infected horses. During the past 30 years, however, due to constant testing of horses and eradication of infected animals, this disease entity has been rare in this country. The only case known by the writers to have occurred in the United States in recent years was described by Herold and Erikson [1] in 1938. The disease occurs more frequently in Russia, the Balkans, and parts of Asia and Africa where veterinary control measures are less stringent or non-existent.

A number of accidental infections have been recorded in the past among laboratory workers.[2, 3, 4, 5] The disease as it occurs in man, either from animal sources or as a laboratory infection, has in turn been divided into two clinical forms, namely acute and chronic glanders. Acute glanders is usually rapid in onset and is fatal in 10 to 30 days. It may appear as a bronchopneumonia or a lobar pneumonia, with or without bacteremia, or a generalized pyemia. The prognosis in the severe acute form is usually grave and the mortality has been reported as approaching 100 per cent.[1, 6] Robins [3] points out the possibility that the majority of human glanders cases may have been included in mortality statistics under some other diagnosis. It is further possible that milder or even sub-clinical cases have gone unrecognized and that their inclusion would thereby reduce the over-all mortality in this disease. The diagnosis of glanders has usually been made by culture of blood [7] or external lesions, by serological methods, and by skin tests.[4, 8] Such treatment as has been reported in the literature appears to have been almost completely ineffective.[9] No report has been found on any trial of sulfonamides or antibiotics.

Six cases of glanders are reported herein. These occurred within the space of one year among personnel involved in laboratory research work with *Malleomyces mallei*. Though this organism was not isolated in any of these cases, it may be of interest that four of these individuals (cases 1, 2, 3, and 4) had been handling a strain † of relatively low virulence (M.L.D. for hamsters 20 to 30 organisms) prior to infection. Patients 5 and 6, however, were probably exposed to a more virulent strain ‡ (M.L.D. for

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† Isolated from the lungs of horses in 1942, and obtained from the type collection of the China Natural Epidemic Prevention Bureau.

‡ Strain 3873, isolated from a fatal human case in China in 1944.

hamsters 5 organisms) introduced into the laboratory a short time before the onset of their illness.

Studies have been made on methods of specific laboratory diagnosis,[9, 10] and on chemotherapy of the experimental disease in animals.[11] With regard to the first of these problems, effective methods have been developed for isolation of *M. mallei*. Agglutination and complement fixation tests were studied and one or more titrations were run on each individual working in our laboratory. It was found that normal human sera agglutinated *M. mallei* in dilutions up to 1:320, but did not fix complement.[10] Sera from 35 cases of primary atypical pneumonia, etiology unknown (so-called "virus pneumonia") gave low titered agglutination and negative complement fixation reactions with these antigens. This was an important factor in the differential diagnosis of the six cases under consideration. Agglutinin titers higher than 1:320 were therefore considered diagnostic. Furthermore, a progressive rise in titer in the same individual from negative to 1:320 appeared to be of some significance. The complement fixation test was a less sensitive index, but was more specific. When positive in dilutions of 1:20 or higher, it was diagnostic of infection with *M. mallei*.

Another diagnostic aid was found in a modification of the mallein skin test, permitting its safe use in humans. One-tenth (0.1) c.c. of commercial mallein in a dilution of 1:10,000 was injected intradermally into the skin of the forearm. The test was read at 24 and 48 hours. During the course of the research program, skin tests were performed on a total of 38 normal individuals. Four of these gave a reaction measuring 3 to 7 mm. in diameter after 24 hours, which faded almost completely after 48 hours. It was found that specific positive tests, encountered in the five patients who reacted, reached maximum erythema after about 18 to 24 hours and faded only slightly if at all by the end of 48 hours. The erythema was usually seen to be 10 to 20 mm. in diameter when the test was positive. No systemic symptoms were associated with any of the routine tests. For experimental purposes, however, six months after his recovery, patient 1 was given 0.2 c.c. of a 1:10,000 dilution of commercial mallein intradermally, representing twice the normal skin test dose. During the first 24 hours following injection, he experienced a mild systemic reaction, consisting of fatigue, malaise, chilly sensations and generalized aching. He noted no temperature elevation. The erythema attained an area of 20 by 45 mm. within 36 hours and had faded somewhat after 48 hours. This was the only systemic reaction noted in any of the subjects upon whom skin tests were performed.

Sulfadiazine has been found to be an effective therapeutic agent for both glanders and melioidosis (*M. pseudomallei*, Whitmori) in experimental animals.[11] Fifty per cent of infected hamsters recovered when given the full therapeutic dose of sulfadiazine for seven days. Twenty days of chemotherapy at full dosage gave 100 per cent recovery. The infection was fatal in 100 per cent of the untreated animals. These figures were the basis for

subjecting each of the last four patients in this series to a total of 20 days of chemotherapy.

### Case Reports

*Case 1.* W. R. M., a 29 year old physician, was admitted to the hospital for the first time on November 27, 1944. His past history was unremarkable, except for a healed Ghon lesion, demonstrable by roentgen-ray, in the left lung field. His last positive skin reaction to old tuberculin had been in 1943.

For the six weeks preceding his illness he had been engaged in research on *M. mallei.* Approximately two weeks prior to his admission, a technician dropped a flask containing a virulent suspension of *M. mallei.* The laboratory was promptly decontaminated. The patient and one other worker (case 2) who was also in the room later developed glanders. At no time did the technician have any evidence of specific infection.

During the two weeks before admission, the patient noted generalized aches and pains, and afternoon temperature elevation to 99.3 or 99.4° F. Two days before admission, he developed a continuous sharp stabbing pain in the right middle chest, aggravated by breathing and relieved by lying on the right side.

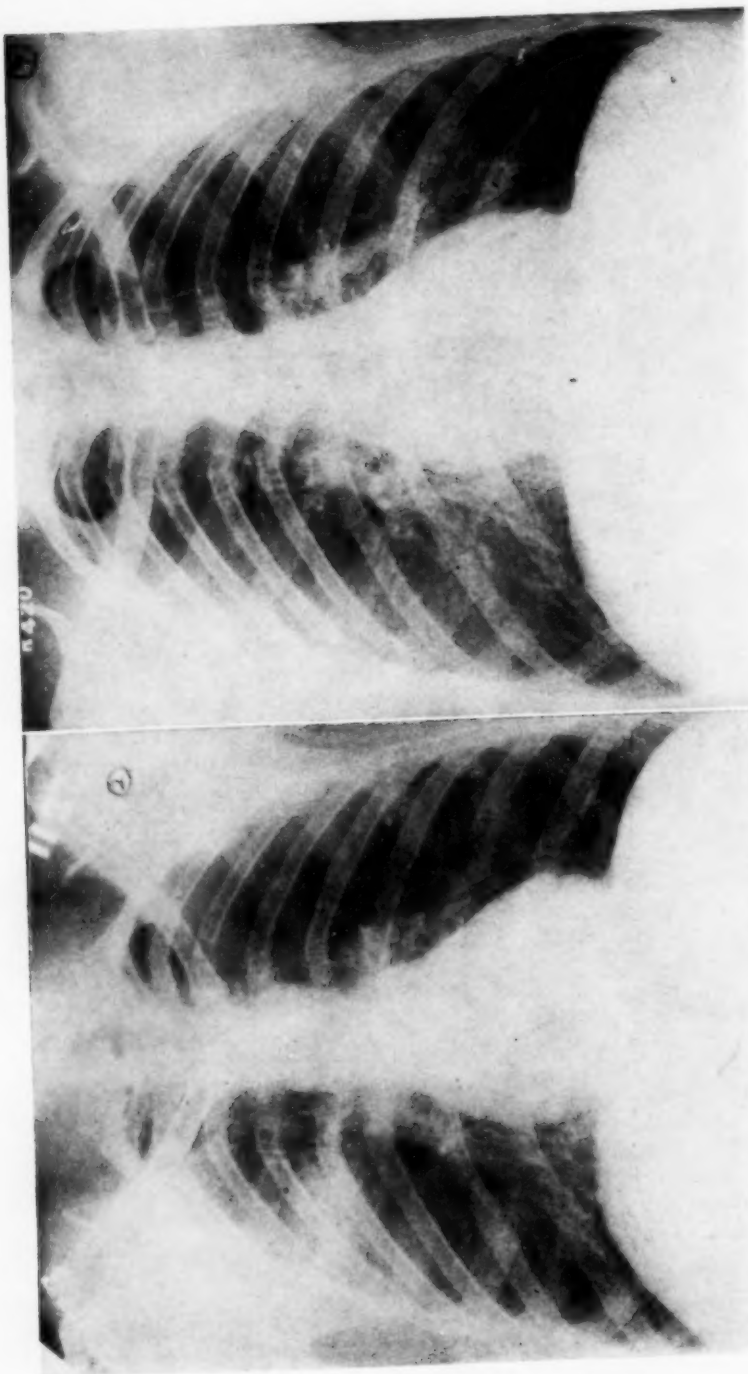
*Course in the Hospital* (First admission). On physical examination, the patient appeared to be fatigued and moderately dehydrated. There were tender glands in the right cervical triangle. Examination of the chest revealed an area of relative dullness and slightly tubular breathing over the posterolateral aspect of the right side of the chest. No friction rubs or râles were heard. There was definite splinting of the respiratory excursions on the right. The abdomen was soft; and the liver and spleen were not felt. The remainder of the physical examination was negative.

The blood on admission showed 6,400 white blood cells per cu. mm., 60 per cent neutrophiles, and 40 per cent lymphocytes. A blood culture was sterile. Three urinalyses during hospitalization were unremarkable. Subsequent blood studies showed no essential change. Two tests for cold hemagglutinins and heterophile sheep cell antibodies were negative. A roentgen-ray film of the chest on admission (figure 1A) showed an area of increased density in the right upper lobe which was roughly circumscribed, and in appearance suggested an early lung abscess. In addition, Ghon lesions were demonstrated in the periphery of both lung fields. A film taken one week later showed no change.

The patient's symptoms subsided on bed rest and supportive therapy. His temperature rose only twice to 99° F., and he was discharged on December 2, 1944 after 48 hours of normal temperature. Up to that time, there had been no serological evidence of specific infection.

*Subsequent Course.* On discharge from the hospital, the patient remained at home for one week, and again noted occasional slight afternoon temperature elevation, not over 99.4° F. During the subsequent days, he gradually resumed his work, and by December 19, 1944 was able to work a full day without temperature elevation or undue fatigue. Two chest films, on December 4 and December 11, 1944, respectively, showed no change in the appearance of the lesion in the right upper lobe. A film on December 20, however, 18 days after discharge, showed definite diminution in its size. Four complete blood counts in this interval showed persistent leukopenia and relative lymphocytosis of 40 to 50 per cent. On January 3, 1945, the patient developed symptoms typical of a common cold, with moderately productive cough and laryngitis. No temperature elevation was noted. The white blood count was 5,600 per cu. mm. with 55 per cent neutrophiles and 45 per cent lymphocytes. A chest film showed further diminution of the lesion previously noted.

A skin test with 0.1 c.c. commercial mallein in a dilution of 1:10,000 was positive on January 9, 1945. Tests on normal controls were entirely negative. The serum



B

A

FIG. 1. A. Case 1. On admission, 14 days after onset of symptoms.
B. Case 1. Eighty days after onset of symptoms.

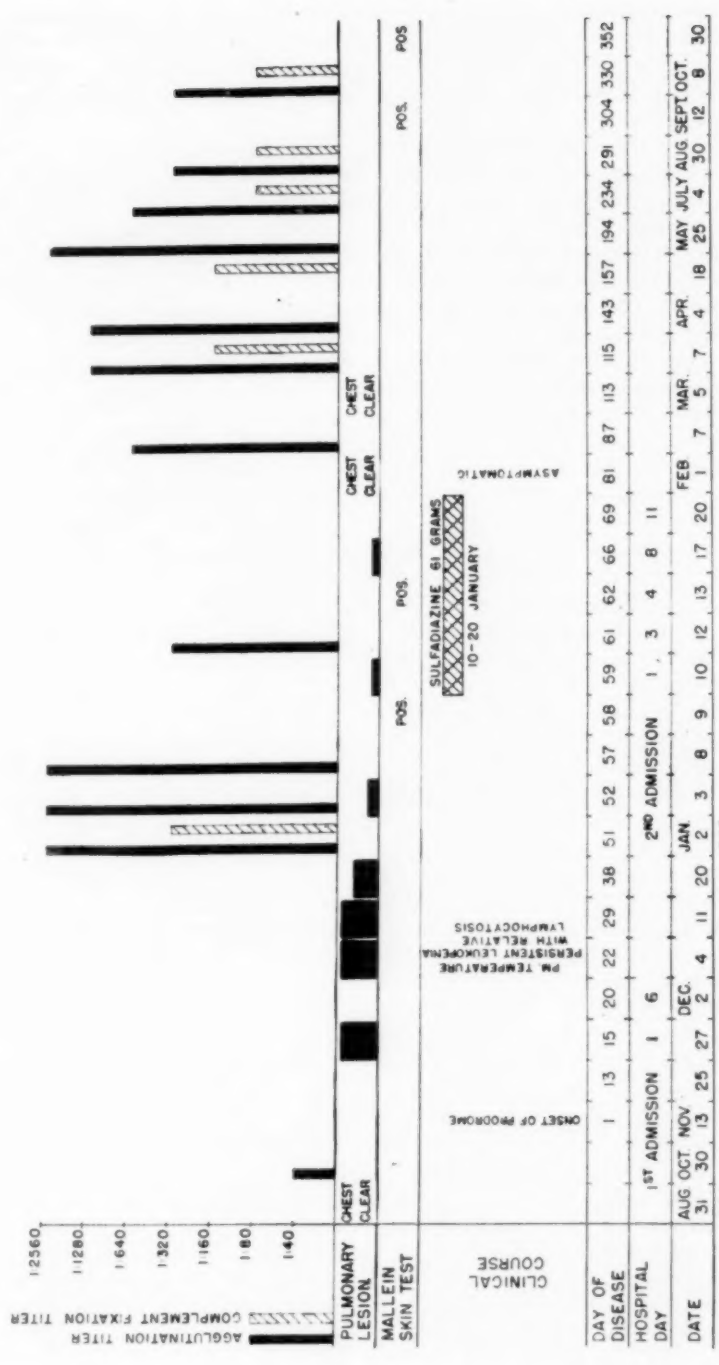



CHART 1. Case 1.

titer of agglutinins for *M. mallei* had risen to 1:2560, and the complement fixation titer was 1:320. On the basis of the positive skin test and the serological evidence of infection, a diagnosis of glanders was made, and the patient was readmitted on January 10, 1945 for treatment. He had no complaints, and physical examination was entirely negative.

*Course in the Hospital* (Second admission). The patient was given sulfadiazine by mouth, 4 grams initially and 1 gram every four hours thereafter, over a 10 day period, for a total dose of 61 grams. A blood sulfadiazine level of 9 to 11 mg. per cent was maintained. The blood continued to show a slight leukopenia and relative lymphocytosis, but without abnormal elements. A blood culture taken before initiation of chemotherapy was sterile. Several attempts to find the suspected organisms in the sputum by culture on crystal violet agar failed. The serum contained no cold hemagglutinins, but the agglutinin titer for *M. mallei* remained elevated.

A chest film taken on admission showed slight residual increased density in the right upper lung field, there having been definite clearing since the last film, taken on January 3, 1945. A film taken one week later showed no change.

*Subsequent Course.* Following discharge and with one week's rest at home, the patient continued to improve, and had no further symptoms. Two subsequent chest films taken on February 1, 1945 (figure 1B) and March 5, 1945 respectively, showed complete clearing of the right lung field. The serum titer of agglutinins and complement fixing antibodies for *M. mallei* remained elevated up to 10 months after onset of illness; but within six more months had become negative. At this time, 16 months after illness, the mallein skin test was still positive.

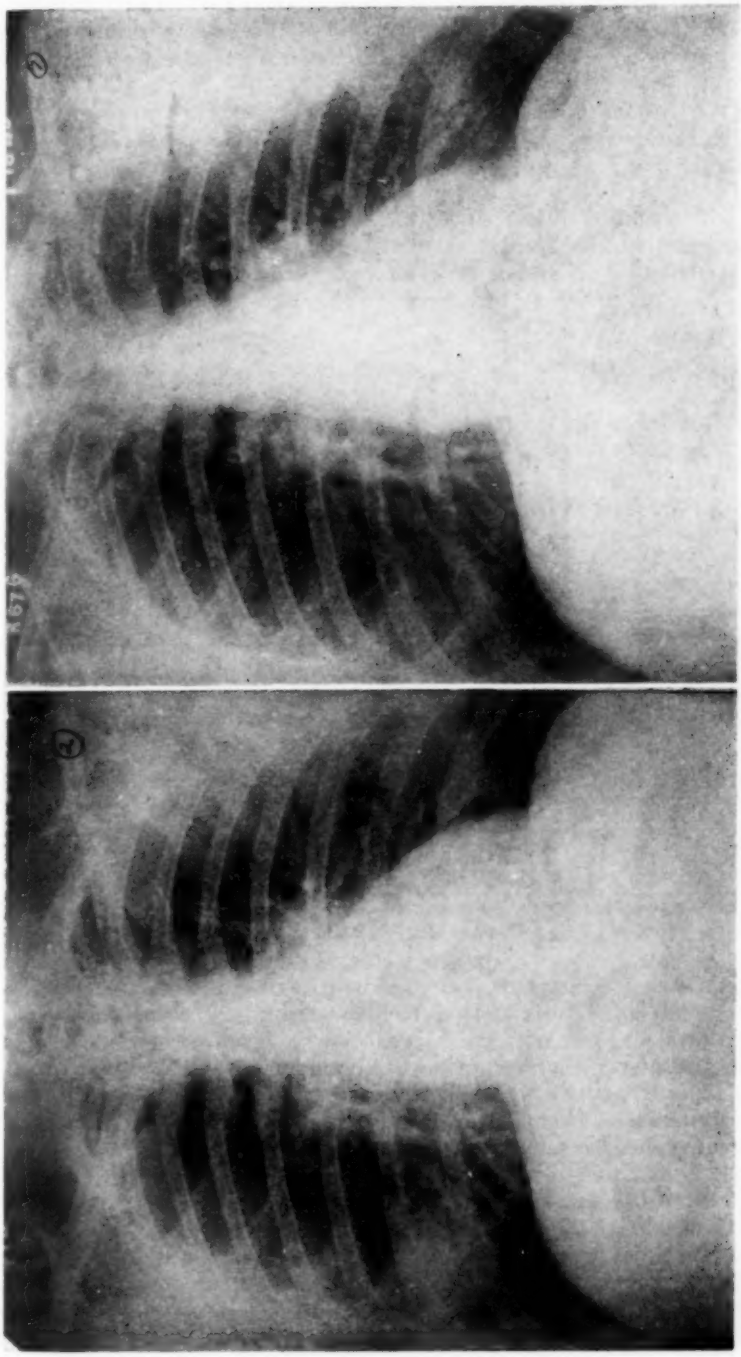
*Case 2.* L. C., a 26 year old Doctor of Public Health, was admitted to the hospital for the first time on November 27, 1944, simultaneously with patient 1.

Since September 1944, he had been engaged in the same research program on *M. mallei.* During the 10 days prior to the onset of his illness, he had handled large amounts of suspension of this organism during the preparation of vaccines. He was present during the laboratory accident described in connection with Case 1. Two weeks prior to admission, the patient noted the onset of muscle pains, some elevation of temperature, and undue fatigue. One week before admission, his temperature rose to 100° F., and he noted progressive increase in symptoms.

*Course in the Hospital* (First admission). Complete physical examination was entirely negative. The total white blood cell count was 5,000 per cu. mm., with 70 per cent neutrophiles, 26 per cent lymphocytes, and 4 per cent monocytes. Urinalysis was negative. A roentgen-ray film of the chest (figure 2A) showed a roughly circumscribed area of increased density in the periphery of the right lower lung field, similar to the lesion seen in Case 1. The appearance of this lesion likewise suggested an early lung abscess.

The patient was virtually afebrile throughout this period of hospitalization, and he noted no symptoms. Blood cultures taken at this time were sterile. Two total and differential white blood cell counts were within normal limits and a test for cold hemagglutinins was negative. The patient was discharged on the eleventh hospital day, 25 days after the onset of his illness.

*Subsequent Course.* Following discharge, the patient remained at home for four days. His temperature remained normal; but he noticed a slight nocturnal cough and small amounts of mucopurulent sputum. Four days after his discharge from the hospital, he resumed working for half days, noting elevation of temperature to 99° F. His cough persisted, and he was subject to undue fatigue. A chest film on December 18, 1944 showed a slight regression of the lesion noted on previous occasions. By December 26, 1944, the patient was working full time, and noted regular afternoon temperature elevations to 99.4 or 99.6° F, his respiratory symptoms persisting. On January 2, 1945, the patient's serum titer of agglutinins for *M. mallei* was found to be 1:2560, the only previous determination, on October 30, 1944, having been within



A B

FIG. 2. A. Case 2. On admission, 14 days after onset of symptoms.
B. Case 2. Sixty-seven days after onset of symptoms.

normal limits. On January 9, 1945, a skin test with 0.1 c.c. commercial mallein in a dilution of 1:10,000 was positive. On the basis of the positive skin test and the serological evidence of infection, the patient was readmitted for treatment on January 11, 1945.

*Course in the Hospital* (Second admission). The patient was given sulfadiazine, 4 grams initially, 1 gram every four hours thereafter, over a 10 day period, for a total dose of 57 grams. He remained afebrile and asymptomatic. A blood sulfadiazine level of 9 to 14 mg. per cent was maintained. The white blood cell count continued to be normal, with a normal differential. Daily urinalysis was negative. The serum titer of specific agglutinins remained elevated. A chest film taken on January 18, 1945, 67 days after the onset of his illness, showed complete clearing of the right lung field (figure 2B). The patient was discharged on January 20, and resumed normal activity.

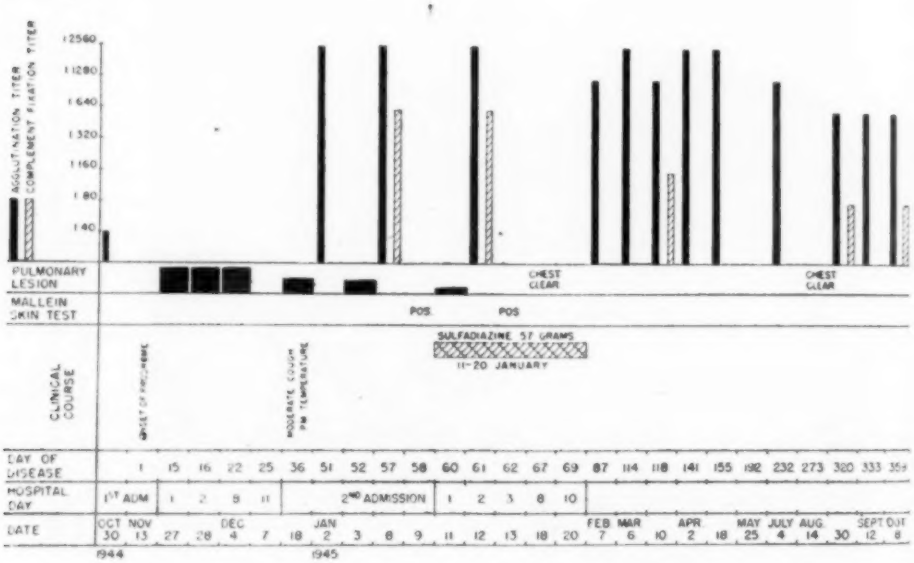
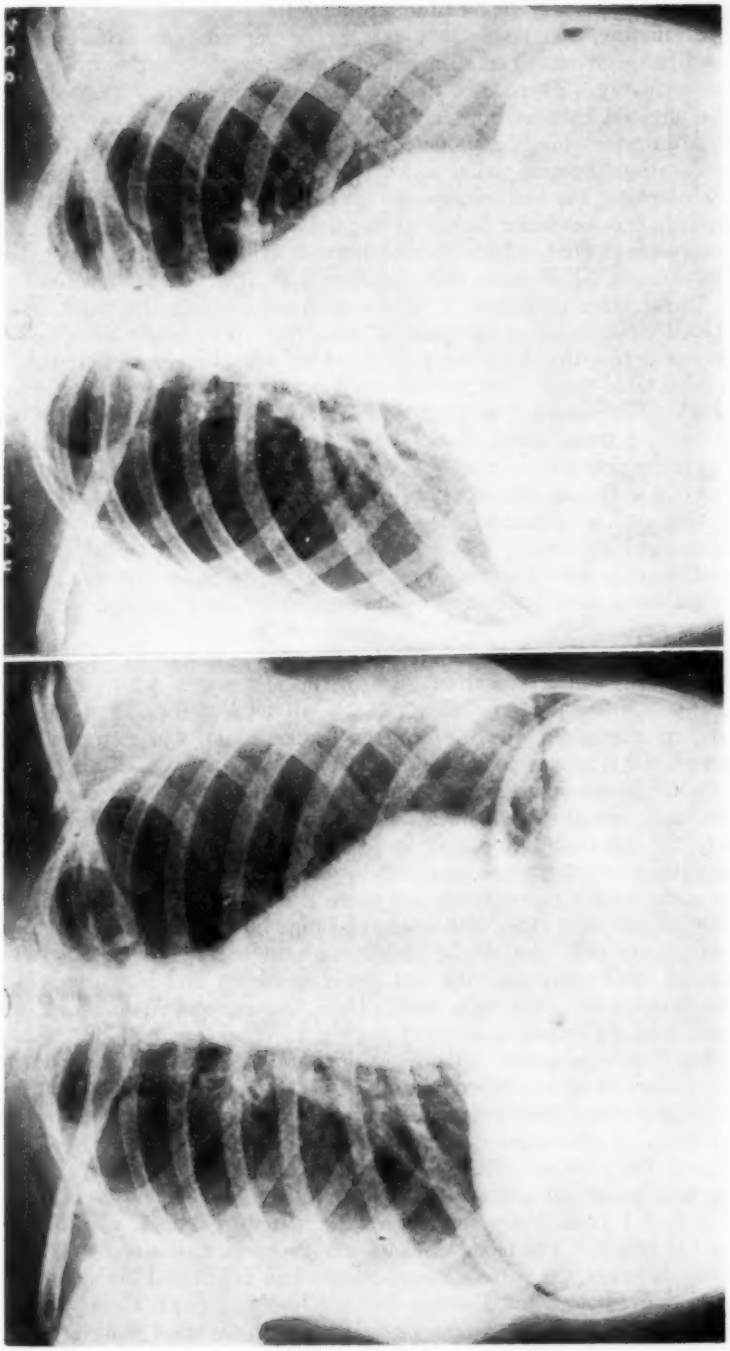



CHART 2. Case 2.

*Subsequent Course.* The patient had no recurrence of symptoms at any time. He contracted two mild upper respiratory infections during the ensuing two months. Chest roentgen-rays on each of these occasions were negative, and blood studies showed no abnormalities. The serum titer of specific agglutinins remained elevated, and skin tests repeated at long intervals remained positive, up to nine months after recovery. Sixteen months after illness, the agglutinin and complement fixation titers had become negative, but the skin test was still positive.

*Case 3.* J. F. W., a 28 year old laboratory technician, was admitted to the hospital on April 16, 1945. His past history included known infections with *Brucella abortus* and *Plasmodium falciparum*, in 1938 and 1943 respectively.

In June of 1944, the patient started to work with *M. mallei*, and was engaged in routine laboratory procedures, such as animal inoculation, plating, and serological determinations. He had no known opportunity for exposure other than that attendant upon harvesting and handling large quantities of suspension for the preparation of vaccines. His health had been excellent until his admission to the hospital on April 16, 1945, two hours after the sudden onset of dizziness, nausea, blurring of vision, backache, and chills.



A B

FIG. 3. A. Case 4. Fourth hospital day, five days after onset of symptoms.
B. Case 4. Twelve days after onset of symptoms.

*Course in the Hospital.* Physical examination revealed a temperature of 100.4° F., a pulse of 86 per minute, and respiratory rate of 20 per minute. The patient was well oriented and coöperative. The skin showed generalized hyperkeratosis. There was no lymphadenopathy. There was marked lacrimation and photophobia. The remainder of the physical examination and a neurological examination were negative.

Two hours after admission, the patient started to complain of excruciating headache and his respirations became more rapid. Two hours later, he was found to be hyperventilating, showing marked carpopedal spasm. Neurological examination was otherwise negative. His headache failed to respond to medication or to the removal of 6 c.c. of cerebrospinal fluid, which showed normal dynamics and was negative on examination and culture. Following this short episode of tetany, the patient had a shaking chill. Blood cultures taken at this time were sterile; and thick and thin smears of the blood were negative for malarial parasites. The white blood cell count was 10,200 per cu. mm. with 84 per cent neutrophiles and 16 per cent lymphocytes. Urinalysis and a portable chest roentgen-ray were negative. During the ensuing two hours, the patient's chills subsided, and his temperature rose to 103.8° F. He became nauseated and vomited three times. By midnight, his temperature had subsided to 99.8° F., after profuse diaphoresis, and by morning it was normal.

From the second to the seventeenth days, the patient's course was characterized by afternoon elevations of temperature of moderate degree, occasional headache, and continued malaise. All laboratory work, including repeated blood cultures, total and differential blood counts, stool examinations, serologic studies for enteric pathogenic organisms, for glanders, and for brucellosis, revealed nothing remarkable. Several chest films were negative.

On the twelfth hospital day, also the twelfth day of his illness, he complained for the first time of a dull aching sensation high in the left upper quadrant. Physical examination showed marked tenderness high in the left flank and under the left costal margin. The tip of the spleen was felt on deep pressure, and was extremely tender. During the next six days, he developed moderate spasm over the whole left side of the abdomen, and the tenderness increased. A flat abdominal film was negative. A skin test with 0.1 c.c. commercial mallein in a dilution of 1:10,000 on the eighteenth day became definitely, though slightly, positive in 48 hours. On the evening of the seventeenth day, the patient's temperature rose and by the following morning had reached 103.4° F. His abdominal symptoms became more acute and he obtained only slight relief from lying on the right side, with knees and hips flexed. Physical examination revealed definite spasm over the whole abdomen, most marked over the left half. There was extreme tenderness over the left upper quadrant and into the left flank, with rebound tenderness from the right side. Deep inspiration caused sharp increase in the abdominal pain. Peristalsis sounded normal in character. Blood culture and inoculation of blood into hamsters and guinea pigs failed to reveal the presence of any organism. The white blood cell count and differential were normal. A urinalysis was negative. The patient obtained relief only from morphine in repeated doses, phenobarbital sodium subcutaneously, and external heat.

On the basis of the positive skin test, a tentative diagnosis of glanders was made, and the patient was given sulfadiazine, 5 grams initially intravenously in 1,000 c.c. of normal saline, and 1 gram every four hours thereafter by mouth, for 20 days, the total dose being 125 grams. The blood sulfadiazine level was maintained at 9 to 10 mg. per cent. Within 24 hours, the patient's temperature had fallen and his symptoms and signs had subsided dramatically. During the ensuing five days, these disappeared completely, and he had only slight afternoon temperature elevation daily for the next three weeks. On the twenty-third day, the agglutinin titer for *M. mallei* had risen to 1:2560. The white blood cell count remained normal, occasionally showing a definite leukopenia with moderate to marked relative lymphocytosis. On the fortieth day, the

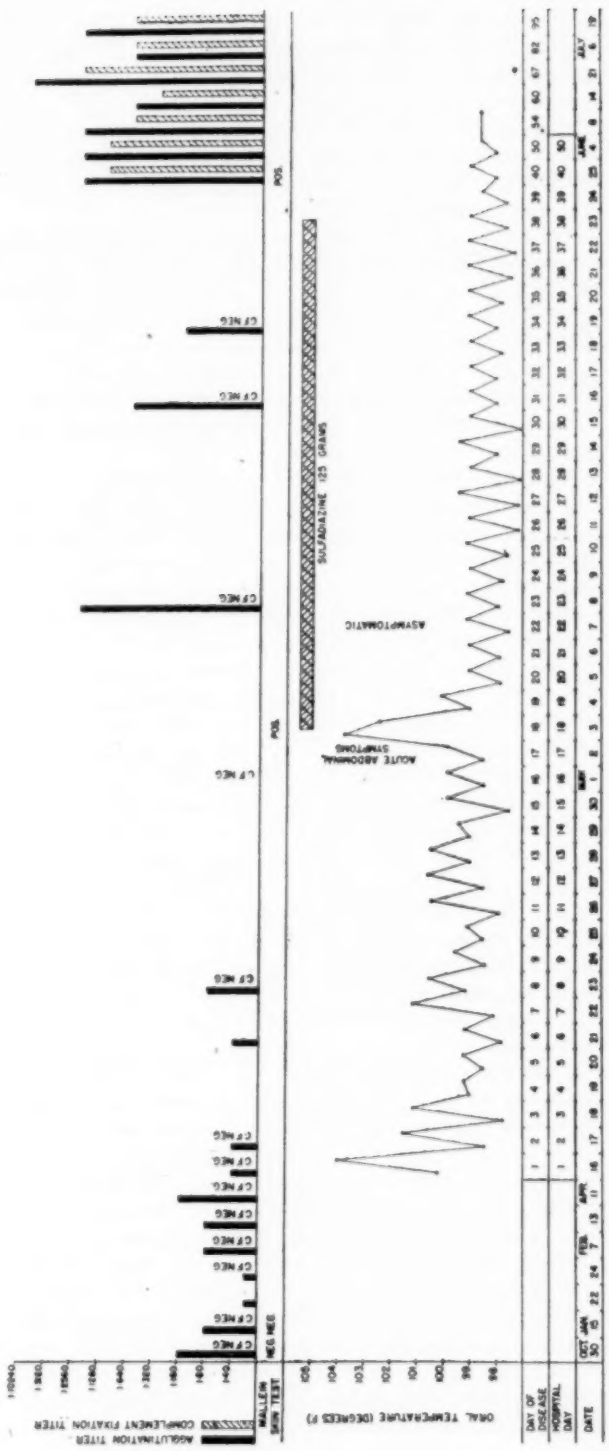



CHART 3. Case 3.

serum complement fixation was found to be positive in a titer of 1:1280, and a skin test was again positive, thereby confirming the diagnosis of glanders. Following the cessation of chemotherapy, the patient remained completely afebrile, and by the time of discharge, was completely asymptomatic.

*Subsequent course.* After three weeks' rest, the patient resumed full time activity, and repeated serologic studies showed continued elevation of specific agglutinin and complement fixation titers. Up to the time of this writing, he has had no recurrence of symptoms and has to all appearances completely recovered.

*Case 4.* C. H. H., a 23 year old laboratory technician, was admitted to the hospital for the first time on February 16, 1945. Her past history and family history were unremarkable. For the six weeks prior to admission, she had been engaged in routine laboratory work with *M. mallei.* On February 13, three days prior to admission, she noted the onset of moderate headache, backache and increasing fatigue; and on February 16, the day of admission, she awoke at 4:30 a.m. with marked stiffness of the neck, and photophobia. She had several shaking chills during the ensuing four hours, and her temperature rose to 102° F. She was admitted to the hospital in a semi-stuporous condition.

*Course in the Hospital* (First admission). On physical examination, the patient appeared acutely ill, and was flushed and dehydrated. She was responsive and cooperative. The neck was supple, and there was slight scleral injection. There was no lymphadenopathy. The remainder of the physical examination was entirely unremarkable. A complete neurological examination was also negative. The temperature was 101.4° F., the pulse 100, and the respirations 22 per minute.

The white blood cell count on admission was 18,000 per cu. mm., 88 per cent neutrophiles and 12 per cent lymphocytes. The urine examination was negative. A spinal puncture performed shortly after admission revealed clear cerebrospinal fluid with normal dynamics. The sugar was 65 mg. per cent; there were seven lymphocytes and the globulin was not elevated. The fluid was sterile on culture. The removal of 6 c.c. did not relieve the severe headache from which the patient was suffering. A chest roentgen-ray taken on admission showed a small, roughly spherical area of increased density in the right upper lung field, at the hilum, measuring approximately 3.5 cm. in diameter. Throat cultures and blood cultures revealed nothing significant.

Because of the rising temperature, the leukocytosis, and the patient's acutely ill condition, she was given sulfadiazine, 5 grams initially intravenously in 1,000 c.c. of normal saline, and 1 gram by mouth every four hours thereafter, for a total dose of 34 grams. She also received penicillin, 60,000 units every three hours for four doses, and 30,000 units every three hours thereafter, for a total dose of 1,050,000 units over the first four hospital days.

The patient's temperature is charted in chart 4. Definite physical signs remained absent, and she continued to be in a semi-stuporous condition, though remaining responsive and coöperative. On the second day, the blood showed a total white cell count of 8,000 per cu. mm., 77 per cent neutrophiles, 23 per cent lymphocytes. The serum titers of agglutinins for *M. mallei* was 1:160, and complement fixation was negative. During this time, she complained of severe, intermittent headache, photophobia, and malaise. Physical examination remained unremarkable except for moderately enlarged and slightly tender lymph nodes in the right anterior and posterior cervical triangles, which had not been felt on admission. A lumbar puncture, performed on the fourth hospital day, showed clear cerebrospinal fluid with normal dynamics, normal sugar, protein, and cellular content. The fluid was sterile on culture and on mouse inoculation. A chest film on the fourth day (figure 3A) showed no change from the film taken on admission. The agglutinin titer on this date was 1:640; and complement fixation remained negative. A blood count showed 5,200 white

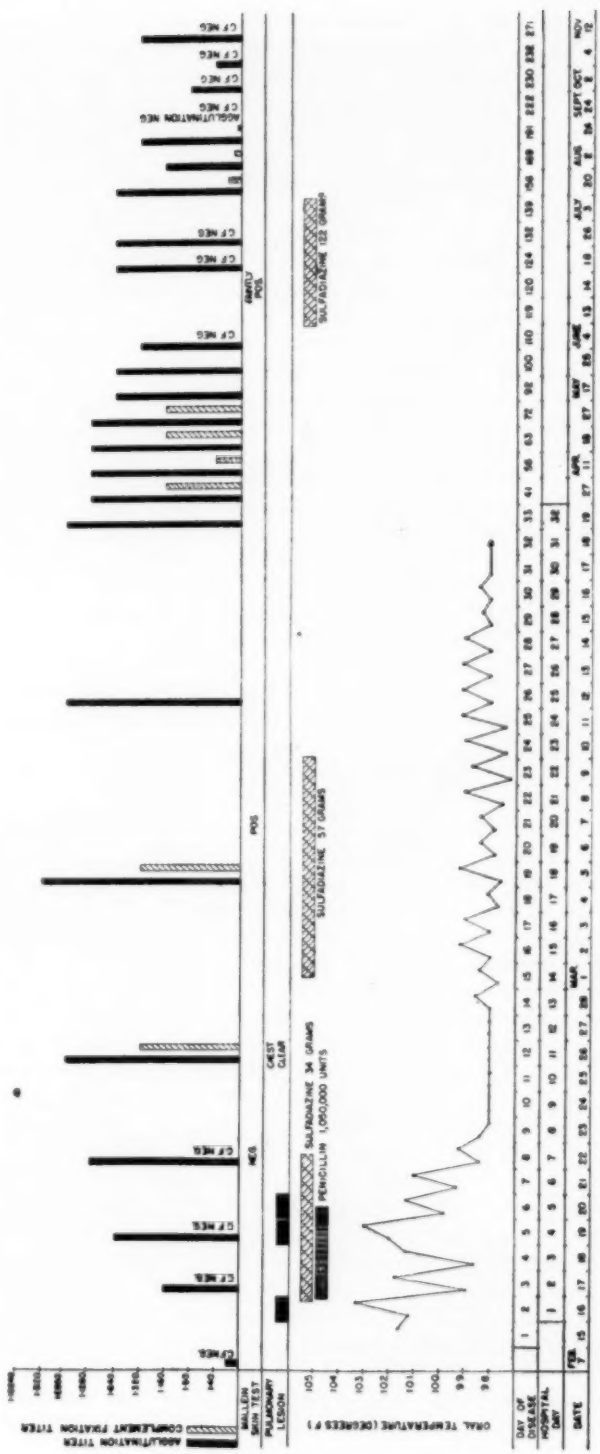



CHART 4. Case 4.

blood cells per cu. mm., 75 per cent neutrophiles, 25 per cent lymphocytes. During the ensuing 48 hours, the patient's temperature subsided gradually, and by the seventh day was normal. Sulfadiazine administration was stopped on the seventh hospital day because of a falling white blood cell count and the appearance of red and white blood cells in the urine. A skin test on the seventh day with 0.1 c.c. commercial mallein in a dilution of 1:10,000 showed no reaction in 24 or 48 hours. The agglutinin titer had risen to 1:1280, complement fixation remaining negative. Tests for heterophile sheep cell agglutinins and for cold hemagglutinins were negative.

The patient continued to be afebrile and asymptomatic except for occasional headache which was relieved by codeine sulfate. By the eleventh hospital day, her titer of agglutinins had risen to 1:2560, thereby supporting the diagnosis of glanders, and suggesting a plausible explanation for the pulmonary lesion seen on roentgen-ray examination. Chest films taken on the twelfth (figure 3B) and eighteenth days, respectively, showed complete clearing of the right lung field.

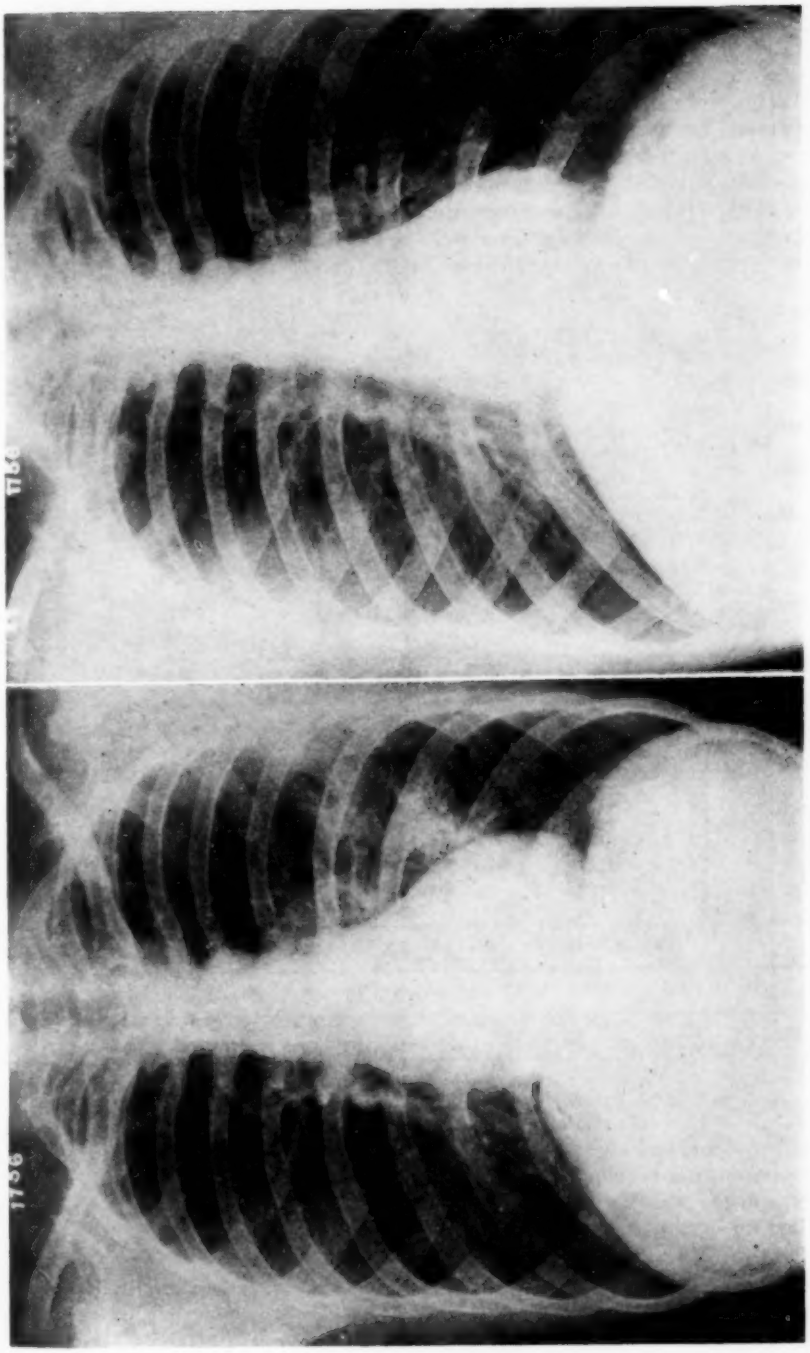
After a test dose of 2 grams of sulfadiazine, to which the patient showed no untoward reaction, administration of the drug was resumed on the fourteenth hospital day, 4 grams initially, and 1 gram every four hours thereafter through the twenty-third hospital day. This represented an additional dose of 57 grams, with the previous period of chemotherapy totalling 91 grams. A blood sulfadiazine level of 9 to 10 mg. per cent was maintained during both periods of therapy. On the twentieth hospital day, the twenty-first day of illness, the skin test was positive; the agglutinin titer had reached 1:5120; and the complement fixation titer was 1:320. The patient was discharged on March 19th, 33 days after the onset of her illness.

*Subsequent Course.* The patient continued to experience moderate fatigue, and noted occasional afternoon temperature elevations. The mallein skin test remained positive; but by June 4, 1945, 10 weeks after discharge from the first hospitalization, the serum titer of agglutinins for *M. mallei* had dropped to 1:320 and complement fixation was negative. Because of persistent, vague symptoms, and the decline in serological response, the patient was readmitted to the hospital on June 9, 1945 for reëvaluation.

*Course in the Hospital* (Second admission). Physical examination on this admission was negative, except for a temperature of 99.4° F. The white blood cell count was 12,000 per cu. mm., 72 per cent neutrophiles, and 28 per cent lymphocytes. The agglutinin titer on June 18 was 1:640, and complement fixation was negative. A chest film revealed nothing abnormal, and inoculation of throat washings and urine into hamsters gave negative results. A mallein skin test was faintly positive. Because of the possibility of continued activity of disease, the patient was started on another course of sulfadiazine, receiving 4 grams initially, and 1 gram every four hours thereafter for a total dose of 122 grams. She had two or three moderately severe asthmatic spells, the etiology of which was obscure. Chest roentgen-ray examinations were consistently negative. Films of the paranasal sinuses and the teeth failed to reveal any abnormalities. She was discharged from this second admission on August 24, 1945, after one week of normal temperature.

*Subsequent Course.* At this time, the patient was given 30 days of convalescent leave, during which she noted occasional afternoon elevations of temperature, but continued to improve steadily. By the end of October, 1945, approximately eight months after the onset of her primary illness, she was completely asymptomatic and showed no sign of active disease.

*Case 5.* C. J. N., a 28 year old veterinarian, had been handling *M. mallei* for approximately one month prior to his admission to the hospital on September 4, 1945. There had been several occasions during the course of his work on which small amounts of infectious aerosol had been inadvertently produced and probably inhaled. On August 20, 1945, 15 days prior to admission, he noted the onset of severe headache.



A B

FIG. 4. A. Case 5. On admission, 16 days after onset of symptoms.
B. Case 5. Sixty-four days after onset of symptoms.

In the ensuing three to four days he also developed severe backache, and by August 27, one week before admission, he had extreme malaise and undue fatigue which persisted for an additional three to four days. On the evening of August 28, six days before admission, his temperature was 102.8° F. At this time he also noted tenderness and swelling of the cervical lymph glands. By August 29, five days prior to admission, he had improved somewhat, but noticed for the first time an aching pain in the left side of his chest, aggravated by deep inspiration. He continued to feel fatigued and the pain in the chest persisted. He did not complain of cough at any time.

*Course in the Hospital.* The temperature was normal. The posterior pharyngeal wall was injected, but there was no exudate. Small tender lymph nodes were palpable in the anterior and posterior cervical chains. Glands were also palpable in the

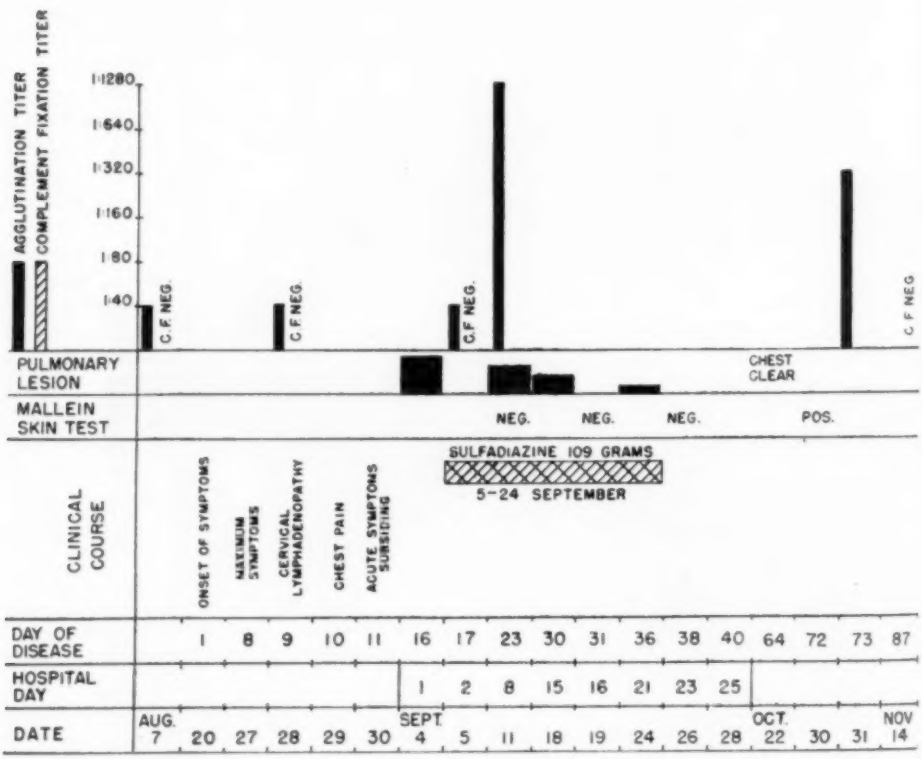
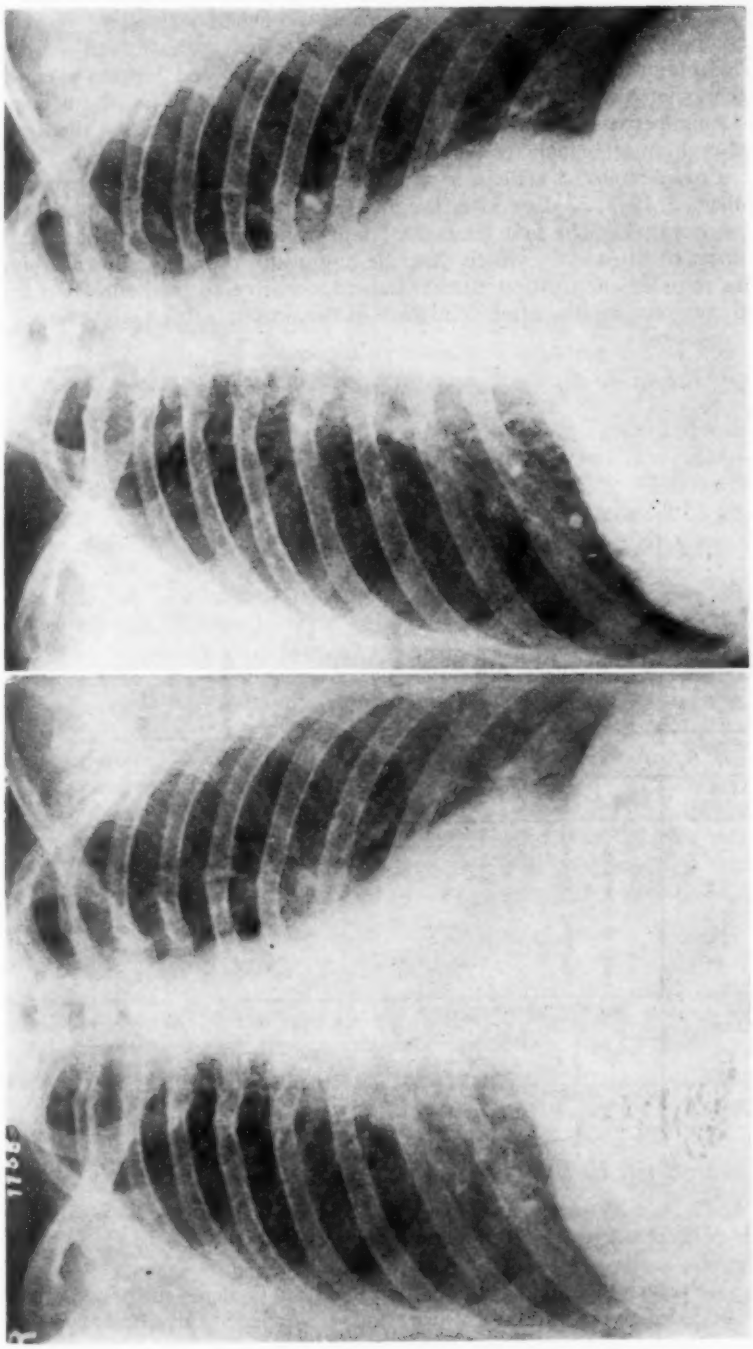



CHART 5. Case 5.

axillary, epitrochlear, and inguinal regions, but were not tender. Physical examination was otherwise unremarkable. The white blood cell count was 7,800, 60 per cent neutrophiles, 40 per cent lymphocytes. Eleven subsequent total and differential blood counts, taken on every second day, were normal except for occasional slight relative lymphocytosis. The agglutinin and complement fixation titers for *M. mallei* are given in chart 5. Cough plates taken on crystal violet agar on admission gave no growth. Tests for cold hemagglutinins and heterophile sheep cell antibodies were negative.

A chest film taken on admission (figure 4A) showed an area of increased density in the mid left lung field, extending to the periphery and involving almost the entire middle third of the left lung field. Films taken on the eighth hospital day, the twenty-



A B

FIG. 5. A. Case 6. On admission, eight days after onset of symptoms.
B. Case 6. Twenty-two days after onset of symptoms.

third day of disease, showed slight reduction in the size of this lesion. There was further reduction in the extent of the lesion during the ensuing six days.

Because of the probability of exposure to and infection with *M. mallei*, the patient was started on sulfadiazine, 4 grams initially by mouth, and 1 gram every four hours thereafter, over 20 days, for a total dose of 109 grams. A blood sulfadiazine level of 10 to 12 mg. per cent was maintained. During the last 10 days of therapy, the patient showed regular afternoon temperature elevations to 99 or 99.2° F. The skin test with 0.1 c.c. of commercial mallein in a dilution of 1:10,000 did not become positive until October 30, 1945, 72 days after the onset of his illness, one month after discharge from the hospital. The first clear chest film was obtained on October 22, two months after onset of disease, by which time the agglutinin titer had shown a significant rise. The complement fixation titer remained negative throughout. Up to the time of this writing, six months after admission to the hospital, this patient's recovery is apparently complete.

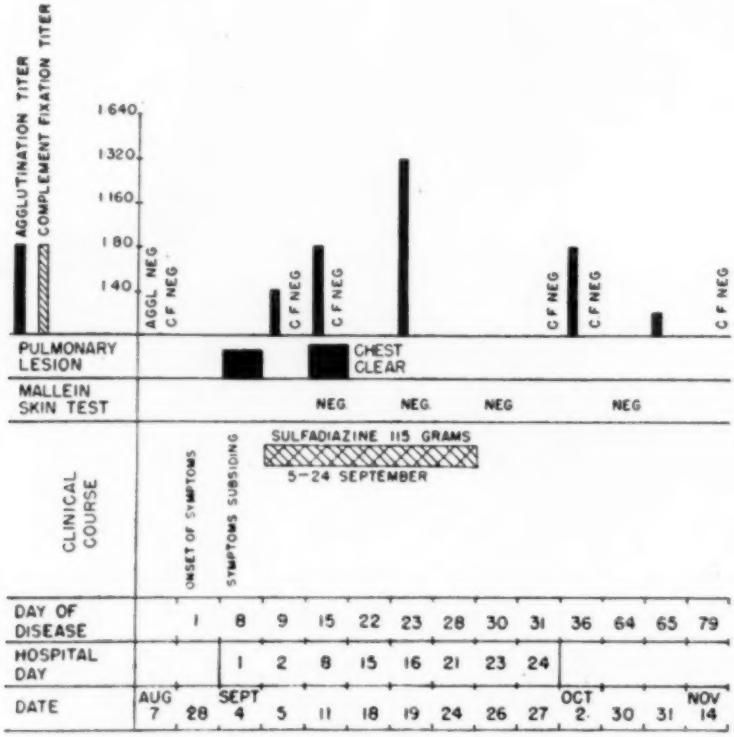



CHART 6. Case 6.

*Case 6.* L. C. F., a 33 year old veterinarian, was admitted to the hospital on September 4, 1945. His past history revealed an attack of undulant fever in 1937, without subsequent relapse.

For the month prior to admission, the patient had been engaged in the same laboratory work as case 5, involving routine culture transfers, inoculations and harvesting of *M. mallei*. He likewise had occasional opportunities for infection in the process of certain laboratory manipulations which may have resulted in the inhalation of organisms. On August 10, 1945, approximately three weeks before admission, he had

received for study a new and more virulent strain of *M. mallei*. On August 21, 10 days later, mass culture of this strain was initiated in the laboratory. The patient knew of no gross laboratory accidents during the two weeks which followed, prior to his hospitalization. He was in good health until about August 28, one week prior to admission, when he noticed that his throat was sore. On the following day, he experienced increasing malaise and noted pain in the left side of his chest, aggravated by deep inspiration. He developed persistent headache, and for two or three days had moderate diarrhea, without other gastrointestinal symptoms. On August 30, five days before admission, he felt feverish, but his temperature was not taken.

*Course in the Hospital.* During the few days immediately preceding his admission, his symptoms had started to subside, and physical examination was entirely negative. The white blood cell count on admission was 7,600, 68 per cent neutrophiles, 32 per cent lymphocytes. The agglutinin titers for *M. mallei* are shown in chart 6. The complement fixation titer remained negative throughout the period of observation. Tests for cold hemagglutinins, heterophile sheep cell agglutinins, and *Brucella* agglutinins were negative.

A chest film taken on admission (figure 5A) showed an area of increased density in the left lower lung field lateral to the pericardial outline, irregular in shape, suggesting, unlike the lesions in the other cases, a pneumonitis. Films on the eighth hospital day, the fifteenth day of disease, showed slight extension of this same area, which, however, by the twenty-second day of disease had disappeared completely (figure 5B).

The patient was afebrile throughout his hospitalization. Because of the close similarity of this case to Case 5, both from epidemiological and clinical points of view, and by reason of his probable exposure to *M. mallei*, he was given sulfadiazine, 4 grams initially, and 1 gram every four hours thereafter. The total dose, over a 20 day period, was 115 grams, and a blood sulfadiazine level of 10 to 11 mg. per cent was maintained. Skin tests with commercial mallein in a dilution of 1:10,000 were consistently negative. The patient was ambulatory during the latter part of his hospitalization and was discharged on September 28, 1945.

*Subsequent Course.* Following discharge, he continued to improve subjectively. The skin test never became positive. The agglutinin titer, by two months after the onset of illness, had fallen to 1:20, complement fixation remaining negative. Up to seven months after illness, this patient has had no further sign of disease.

## Epidemiology

During the period covered by the research program, a total of 22 persons worked in a single, isolated, relatively small laboratory building at various times. Thirteen of these were actually engaged in laboratory work. The other nine were employed in general maintenance. The six patients in this report represent 27 per cent of the total number of people who may have at one time or another been exposed to infection, and 46 per cent of the persons actually working in the laboratories.

The incubation period cannot be accurately determined in any of these cases. In retrospect, however, the patients were able to recall what appeared to have been relatively insignificant incidents during the course of their laboratory work, which may have been the source of their infections. The first two patients were both involved in the same laboratory accident, as has already been pointed out, two weeks prior to the onset of their symptoms.

Ten to 14 days before the onset of their symptoms, patients 1, 2, 3, and 4 had each been engaged in washing the growth of organisms from agar plates during the preparation of vaccines. Although protective clothing was worn and extreme care was exercised, the inhalation of an aerosol may well have occurred. Patient 4 may have been the victim of a technical oversight. After washing growth off of agar surfaces for the preparation of suspensions, she had failed to kill the organisms by heat prior to making up dilutions for standard turbidity measurements. This mishap occurred two weeks before the onset of her symptoms. About two weeks prior to their admission, patients 5 and 6 had been engaged in procedures involving the aeration of cultures by bubbling air or oxygen through liquid medium. They recalled that on one or two occasions the containers had been opened immediately after the air current had been turned off, rather than after a period of delay long enough to minimize the escape into the room of the infectious aerosol in the upper part of the container. It will be recalled that these two patients had been working with a strain of *M. mallei* of greater virulence than that to which the first four patients had been exposed.

If the incidents enumerated above were the occasion for actual exposure in each case, the incubation period would then appear to have been 10 to 14 days for all six patients.

The mode of infection cannot be proved in any case. The usual precautions were taken during all laboratory procedures. Regular check-up studies consisting of culture of air samples and of swabs of tables, benches, refrigerators, incubators, and other equipment, failed to reveal any persistent contamination. Triethylene glycol aerosols were put up in the laboratory rooms during procedures which were thought to be particularly hazardous. All personnel working with the organisms wore special laboratory clothing and were fitted with operating gowns and surgical gloves when handling infectious material, thus minimizing the possibility of infection by other than the respiratory route. The incidents recalled by each patient as enumerated above suggest that there had been opportunity for the creation and inhalation of an infectious aerosol in each instance. These opportunities, furthermore, were supplemented by the fact that all six patients had at one time or another been in the habit of using mouth suction on plugged dilution pipettes and of blowing out the last drop from pipettes calibrated to the tip. The preponderance of pulmonary lesions (five out of six cases) and the various opportunities for respiratory exposure suggest that the respiratory tract was the main route of infection.

## Diagnosis

*Laboratory Findings.* *M. mallei* was not isolated from any of these patients. Blood cultures were taken in all cases on one or more occasions, with both routine medium and special medium designed to enhance the growth of *M. mallei*. Further attempts to isolate the organism by inocula-

tion of blood into hamsters met with no success. Throat washings and sputum, after incubation with penicillin, were cultured on crystal violet agar without positive results.

The diagnosis of glanders was substantiated by a significant and sustained rise in the serum titer of agglutinins for *M. mallei* in five cases, and by a less marked rise in titer in the sixth case. In cases 1, 2, 3, and 4, the complement fixation test also became positive. In the absence of positive complement fixation in the sixth case, the rise in agglutinin titer to 1:320, even though this did not exceed the level encountered in normal sera, was significant, since repeated tests on normal controls had shown no such wide fluctuation.

The only other striking laboratory finding was a persistent leukopenia and relative lymphocytosis. With recovery, the lymphocytosis tended to subside, and the differential count gradually resumed normal proportions.

*Skin Test with Mallein.* The significant serological response in the first five cases was accompanied by a positive reaction to the intracutaneous injection of 0.1 c.c. of commercial mallein in a dilution of 1:10,000. On each occasion, where skin tests were performed on patients in this series, the same test with the same material was performed on individuals who were known to be free of infection. The first and second patients (who had long since recovered) were used as positive controls in testing the last four patients. No false positive results were encountered among the usual negative controls and all of the known positives reacted consistently.

*Roentgen-Ray Findings.* The roentgen-ray findings in Cases 1, 2, 4 and 5 were similar, in that the lesions suggested lung abscess in the early stages, before cavitation and necrosis, being fairly well circumscribed and roughly circular in outline. The lesion in Case 6, however, had more the appearance of pneumonitis, being more diffuse and infiltrating in character. Robins[3] states that the pathological findings in human infections with *M. mallei* constitute anything from a moderate bronchial pneumonia to a focal necrotizing lesion more nearly approximating lung abscess. It is thus apparent that the roentgen-ray findings in Case 6 are not inconsistent with the diagnosis of glanders. There was no evidence by roentgen-ray of pleuritis or pleural effusion. Patients 1, 5, and 6, however, complained of pain which suggested pleural irritation.

## Treatment

All of the patients in this series were treated with sulfadiazine because of its demonstrated efficacy in experimental glanders and melioidosis in animals. Patients 1 and 2 were treated some time after the discovery of their pulmonary lesions, the correct diagnosis being established during their convalescence. Sulfadiazine was given to these two patients with the object of preventing possible spread or exacerbation of disease. There was obviously no opportunity to observe any clinical response to chemotherapy.

In the last four cases, sulfadiazine was given for a total of 20 days because of the indications from the experimental work that this amount of

therapy was essential for 100 per cent recovery in animals. Furthermore, the administration of the drug in these four cases was started nearer or during the acute stage of disease, when the diagnosis of glanders appeared probable. In Case 3, the diagnosis was complicated by a past history of brucellosis and malaria. The acute abdominal signs and symptoms were interpreted as evidence of splenitis or perisplenitis. These manifestations were of interest because of the extensive splenic granulomatous lesions which occur consistently in animals infected with *M. mallei*.[12, 13] The most definite response to treatment was observed in Case 3, who showed a marked drop in temperature and definite symptomatic improvement within 48 hours after the institution of chemotherapy. This clinical response appeared to be significant.

Case 4 also showed a fairly clear-cut clinical response to therapy, though her improvement was not so dramatic as that of Case 3. A second course of sulfadiazine was given in this case because of the recurrence of fever and constitutional symptoms.

In Cases 5 and 6, whose respective courses were almost exactly parallel, chemotherapy was initiated shortly after the acute stage of disease had passed because of the suggestive epidemiologic evidence and the definite pulmonary lesions. Since these two patients appeared to be improving before they received sulfadiazine, it is difficult to assess the therapeutic action of the drug and its effect on the course of disease. It was thus impossible to determine how long treatment should have been continued for maximum benefit. It is of interest that the pulmonary lesions in Cases 5 and 6 showed complete regression at the end of eight and three weeks, respectively, whereas the lesions in Cases 1 and 2 were still visible after more than eight weeks. It will be recalled that Cases 1 and 2 received 10 days of chemotherapy not during the acute stage, but long afterwards, and while the pulmonary lesions though still demonstrable, were regressing. Cases 5 and 6, however, received twice as much treatment, and that chronologically much sooner after the onset of acute illness, while pulmonary lesions were ostensibly at their height.

## Summary and Conclusions

1. Six cases of human glanders are presented in detail.

2. The diagnosis, suspected on the basis of epidemiologic evidence and clinical findings, was substantiated by the results of serum agglutination and complement fixation tests, and response to mallein skin tests in five cases. In the sixth case, the serological data were not clear cut, and the skin test was consistently negative. Because of striking similarity to Case 5, from both clinical and epidemiologic viewpoints, he was considered to be a case of glanders, and was therefore included in this series.

3. All six patients were treated with sulfadiazine because of striking evidence of its efficacy in animals infected experimentally with *M. mallei*. From a study of these cases there are indications that human infection with

*M. mallei* is amenable to treatment with sulfadiazine, though no definite conclusions can be drawn from so small a series. It is clear, however, that sulfadiazine warrants further adequate trial in human glanders.

The authors are indebted to Major H. V. Ellingson, M.C., U.S.A., Post Surgeon, Captain E. S. Miller, M.C., A.U.S., and Captain H. L. Bookwalter, M. C., A.U.S. for assistance in the care and management of these patients. They wish also to express their appreciation to Lieutenant Colonel A. O. Hampton, M.C., A.U.S., Walter Reed General Hospital, for reviewing the roentgen-ray films, and to Captain R. A. West, Sn.C., A.U.S., 1st Lieutenant F. M. Schabel, Sn.C., A.U.S., and Ensign L. Cravitz, H(S), U.S.N.R. for much of the laboratory work.

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# CASE REPORTS

## CUTANEOUS DIPHTHERIA WITH TOXIC MYOCARDITIS: REPORT OF FATAL CASE WITH NECROPSY FINDINGS *

By Saul Solomon, Lieut. Col., M.C., A.U.S., F.A.C.P., and Carl W. Irwin, Capt., M.C., A.U.S.

In the surgery of war wounds, one must expect to lose a number of patients whose injuries are extensive. However, when the injury is in itself trivial and a fatal complication results, the outcome is apt to disturb the equanimity of those who have attended the case and to point the moral that there are no trivial war wounds. Every case is potentially serious and the results unpredictable.

The case we wish to report is that of a soldier who developed abrasions of the buttocks from riding a mule. These abrasions became infected with Klebs-Loeffler bacilli, and he died of toxic myocarditis.

Cutaneous diphtheria as well as wound infection by the Klebs-Loeffler bacillus was apparently uncommon on the Western front. The First General Medical Laboratory which received a fair sampling of bacteriologic material from U. S. Army Hospitals in the United Kingdom found only a few cases of cutaneous diphtheria.[1] Reports from the Middle East, however, indicate that the condition was much more frequent there. Cameron and Muir [2] reported a series of 66 cases of cutaneous diphtheria from Northern Palestine. The lesions occurred on unbroken skin as well as on scratches, insect bites, impetigo or other skin lesions. A large percentage of the patients had diphtheria of the nose and throat, and it appears that the cutaneous infection was due to autoinoculation. Twelve of the cases developed paralysis of spinal or cranial nerves usually as a late development. Hunt's [3] experiences in North Africa were very similar. He saw 76 cases of which 19 developed polyneuritis. Two patients developed diphtheritic myocarditis and died. Benstead [4] reported 31 cases of cutaneous diphtheria from India, three of which developed peripheral neuritis. Melchior [5] observed a few cases occurring on various ulcers, burns, and amputation stumps. Myers [6] pointed out that death may occur from respiratory paralysis, Adams-Stokes attacks or myocardial decompensation, and emphasized that once these degenerative sequelae of diphtheria have appeared, treatment with antitoxin has little if any effect on the outcome.

The characteristic chronic diphtheria ulcer is oval with a raised rolled edge and a deep unhealthy base usually covered by a dirty gray membrane. The lesion in our case was quite different, resembling more a superficial weeping and crusting dermatitis. The common chronic sores of diphtheria are particularly indolent and may take months to heal despite therapy. Although this may be time-consuming, it is not the chief reason for the necessity of early bacteriologic diagnosis. The matter is urgent because of the complications that the diphtheria toxin may cause, which are the same whether the infection is in the upper respira-

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tory tract or on the skin. The commonest is peripheral neuritis involving as a rule only the motor nerves. The paralysis nearly always disappears completely in weeks or months. However, the most serious complication and the cause of the majority of deaths in Klebs-Loeffler bacillus infections is toxic myocarditis, which was the cause of death in our case.

The treatment has not changed despite the advent of chemo-therapy. Diphtheria antitoxin must be employed. The dosage is 20,000 to 60,000 units according to Myers,[6] but it is our impression that the higher dose is preferable. One should not wait before commencing treatment, because once the toxin has been fixed in the peripheral nerves or myocardium, the damage cannot be undone. As a British writer [7] points out, the medical officer should act on clinical judgment and morphologic appearance of bacteria in smears in deciding whether to give antitoxin. Otherwise by delaying specific treatment until laboratory identification is complete he may himself perpetrate a virulence test on a human subject with irreversible effects. Our case did not receive treatment, since the diagnosis was not made until after his death. Even if he had received antitoxin when first seen by us, it would have been too late, since toxic myocarditis was already far advanced.

The source of the virulent Klebs-Loeffler bacilli may be the patient's own upper respiratory tract or that of another patient, the physician, nurse, or attendant. Throat cultures should be taken of the patient and all his contacts. Our patient had the condition before his admission to our hospital, and it is likely that he was infected by a carrier when his lesion was dressed. This would be strong argument in favor of keeping wounds covered except when dressings are changed and insisting on masks being worn by attending personnel at such times.

### Case Report

A 25 year old white soldier who was wounded in action on Aug. 8, 1944 by shell fragments, sustained lacerations of the right thigh, right leg, and right thumb. He was treated in an Aid Station where the wounds were debrided, and he was given sulfathiazole, a total of 6 gm. in 24 hours. He also complained at that time of abrasions of both buttocks, incurred from riding a mule. The abrasions were cleaned and appeared insignificant. On Aug. 9, he was transferred to a Clearing Station where it was found that he had a fever of 101.6° F. A diagnosis was made of inguinal lymphadenitis secondary to infection of the lacerations of the thigh. Hot compresses were applied to the right thigh, and the patient received sulfadiazine from Aug. 9 to Aug. 15. On Aug. 16 a diagnosis was made of perineal epidermophytosis, referring to the infected abrasions of the buttocks, and potassium permanganate compresses were applied. The patient was transferred through several more installations before reaching this hospital on Aug. 20 at 2:30 p.m. as a litter case.

Physical examination on admission showed healing wounds of the right thigh, right leg and right thumb. On the lower medial surfaces of both buttocks there were superficial crusted lesions, each approximately two inches square, covered with a slight tan-colored exudate. The temperature by mouth was 96.8° F., pulse 68 and respirations 16. The heart was regular, not enlarged, and no murmurs were heard. The rest of the examination was essentially negative. The red cells numbered 5,760,000 with 95 per cent hemoglobin. Some of the red cells showed stippling and polychromatophilia, and a few normoblasts were seen. The white cells numbered 27,000 with 65 per cent mature polymorphonuclear cells, 5 per cent "stab" forms, 23 per cent lymphocytes, 6 per cent monocytes and 1 per cent basophiles. His injuries were not

serious, and no special attention was paid to him until the following afternoon, when it was noted that he appeared pale, cyanotic, and somewhat dyspneic. The neck veins were distended, the heart sounds were muffled, the ventricular rate was 40 and the blood pressure could not be obtained. An electrocardiogram taken at 5:30 p.m. showed complete auriculoventricular block with a ventricular rate of 40 and an auricular rate of 76. There was also an intraventricular conduction defect of the left bundle branch type (see figure 1).

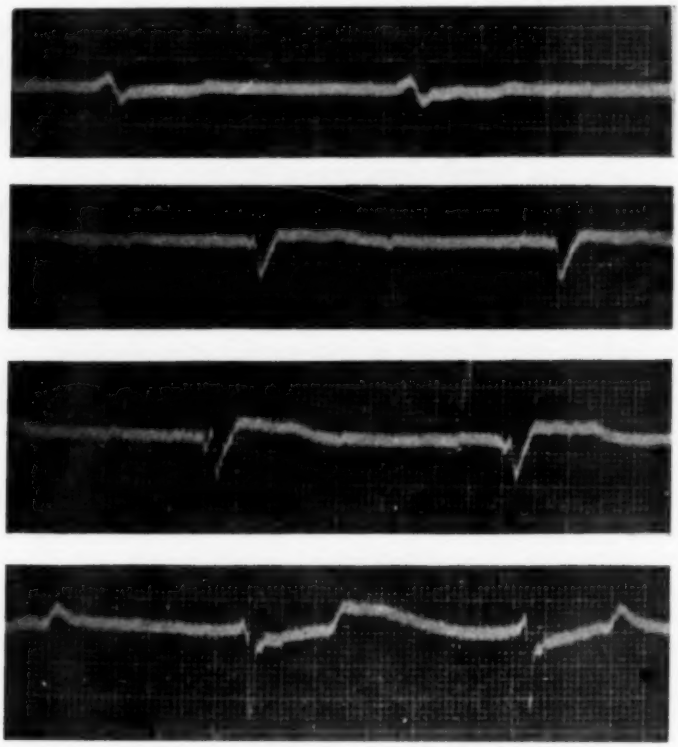

FIG. 1. Electrocardiogram taken Aug. 21, 1944 at 5:30 p.m.

The etiology of this severe cardiac condition was puzzling. There was no evidence of rheumatic heart disease and no history of exposure to any known toxin. The possibility of coronary embolus with closure of a vessel supplying the septum was considered. The possibility of diphtheria was also thought of, but the nose and throat appeared normal and the wounds did not appear infected. A direct smear of the abrasions of the buttocks showed considerable debris, a few pus cells, a few cocci, and a few bacilli which could not be identified. Culture of the abrasions was made on Loeffler's blood serum, and on the following day was reported as showing a pure growth of Klebs-Loeffler bacilli. These proved to be virulent to non-protected guinea pigs.

An electrocardiogram taken at 9:30 p.m. showed a complete heart block with a ventricular rate of 72. The ventricular complexes were bizarre and varied in duration from .25 to .42 sec. (figure 2), and this was interpreted as an agonal type of tracing. At 10:30 p.m. the patient suddenly became more dyspneic and cyanotic, and the neck

veins were markedly distended. Death occurred shortly after, approximately 32 hours after admission.

The necropsy was done by Lt. Col. Jesse E. Edwards. The heart weighed 440 grams. The ventricular myocardium appeared firm and deep red. The interventricular septum showed a patchy mottling. On microscopic examination there were seen in both ventricles and the interventricular septum large and small foci in which the myocardial fibers had disappeared leaving only stroma and a small infiltrate of lymphocytes, plasma cells, and macrophages. Portions of necrotic fibers still remained in most of these foci.

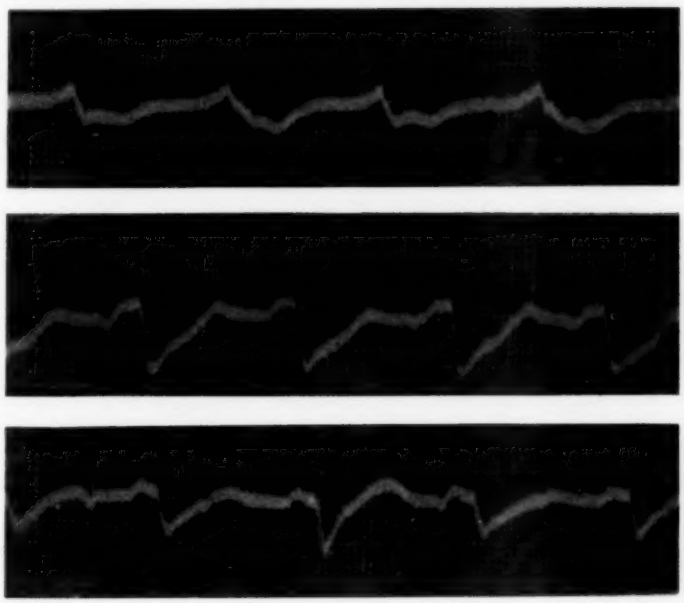

FIG. 2. Electrocardiogram taken Aug. 21, 1944 at 9:30 p.m.

A section taken from the infected abrasion of the buttocks showed denudation of the skin with a superficial but active cellular infiltrate of polymorphonuclear cells in the corium. There appeared to be very little fibrin in the exudate. Bacterial colonies were present on the surface and within the exudate. There was pulmonary congestion and edema of both lungs.

## SUMMARY

A case is reported of cutaneous diphtheria with fatal toxic myocarditis. The diphtheritic infection was engrafted on what otherwise might have been trivial abrasions of the buttocks. The diagnosis was not established until after the patient's death. This failure may have been in part due to the fact that he passed through six installations during the course of his illness and did not remain long at any one of them. Moreover the lesion was not the characteristic deep diphtheritic sore, and no distinct membrane was ever noted. One should keep in mind the possibility of cutaneous and wound diphtheria even though the characteristic picture may not be present. Cultures of wounds and skin lesions

which fail to heal promptly should be a routine procedure. Prophylactically, the wearing of masks when dressings are done is advisable, since diphtheria infection is nearly always conveyed by droplets.

Cutaneous diphtheria was apparently rare on the Western front although reports of many cases have come from Africa, the Middle East and India. Early diagnosis is important because of the complications which the diphtheria toxin may cause. The commonest of these is peripheral neuritis, but the most serious complication, and by far the most common cause of death is toxic myocarditis. In view of this diphtheria antitoxin should be given as soon as the diagnosis is suspected. Delay is dangerous since once the toxin has been fixed in the peripheral nerves or myocardium antitoxin is of no avail.

*Addendum:* Since this report was written, we observed another case of cutaneous diphtheria in a patient with a shell wound near the left ankle. The wound developed thick rolled edges and a deep unhealthy base covered by a yellowish-gray membrane, which is the usual picture of wound diphtheria. Cultures and virulence tests were positive. The source of infection was not discovered. Throat cultures from the patient nurses, attendants and medical officers were negative. He received a total of 80,000 units of diphtheria antitoxin. No complications developed, and within a week the membrane disappeared and wound healing progressed uneventfully.

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# VENTRICULAR TACHYCARDIA WITH ELECTRICAL ALTERNANS RESULTING FROM DIGITALIS EXCESS *

By J. H. Currens, M.D., *Boston, Massachusetts* and R. C. Woodard, M.D., *Miami, Florida*

The electrocardiographic picture of ventricular tachycardia is usually quite characteristic, and although the rhythm is as a rule slightly irregular, the ventricular complexes are quite uniform in appearance. Regular alternation in the direction of the QRS complexes during ventricular tachycardia has been reported by various authors, and, in the majority of cases digitalis intoxication has been responsible for the tachycardia.[1-4] We should like to present the following case report and electrocardiogram demonstrating alternation in the amplitude of the

* Received for publication September 14, 1945.

QRS complexes without an alternation in the direction of the complexes. This has the appearance of electrical alternans and is presented because of this unusual variety of ventricular tachycardia.

## Case Report

Mrs. C. A. W., a 75 year old married woman, was admitted to the hospital May 19, 1944 because of shortness of breath and dependent edema. For 20 years she had been troubled with recurrent arthritis of the fingers, knees and elbows, and this had resulted in slight deformity of the fingers, characteristic of rheumatoid arthritis. Eleven years before (1933) she was seen by Drs. Sprague and White in Boston who had made a diagnosis of aortic stenosis. She was started on digitalis at this time and has continued taking one tablet (0.1 gm.) each day. For five years mild diabetes mellitus had been present, and she had recently been taking 10 units of protamine insulin daily.

The patient was in good health and the cardiac reserve was quite good until five months before entry when she developed moderate dependent edema associated with some dyspnea which subsided spontaneously after one week of bed rest. Three weeks before entry the dependent edema reappeared, and dyspnea and orthopnea became bothersome. About 10 days before entry her digitalis dosage was increased to two tablets a day (0.2 gm.) in an effort to alleviate the dyspnea and edema.

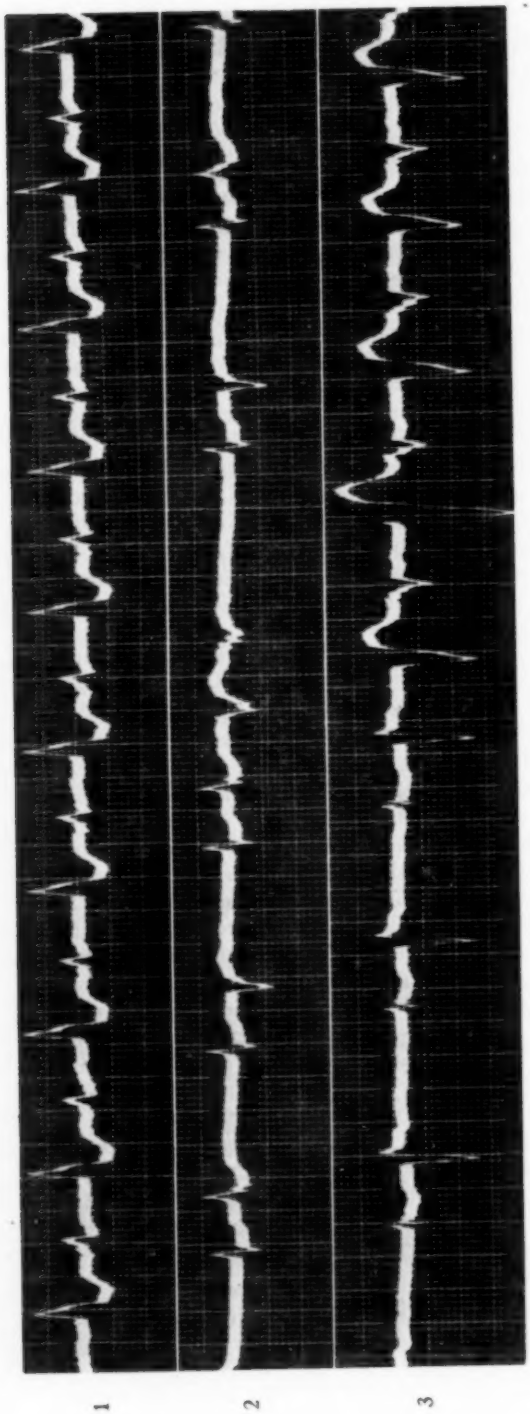
Physical examination revealed a mild cyanosis of the face and lips, and the cervical veins were pulsating and moderately distended when the patient was erect. The heart was enlarged, and the apical impulse was in the sixth interspace in the anterior axillary line. The rhythm was totally irregular at an average rate of 95 except for short runs of regular tachycardia of short duration at a rate of about 145. There was a loud systolic murmur heard over the precordium, about equally well heard at the aortic and mitral areas but not well heard at the left lung base. No diastolic murmur was heard. The blood pressure was 160 mm. Hg systolic and 80 mm. diastolic. The liver descended four fingers'-breadth, and edema was marked over the sacrum and lower extremities.

Laboratory data revealed normal blood counts, and the differential leukocyte count was likewise normal. Urinalysis revealed a two plus albuminuria but was otherwise negative. An electrocardiogram was made on entry and is illustrated in figure 1. It demonstrates auricular fibrillation with frequent ventricular premature beats and periods of ventricular tachycardia. Electrical alternans is present of varying degree during the ventricular tachycardia.

Digitalis was omitted, and 0.2 gm. of quinidine sulfate was given and repeated each six hours. The following morning pulsus bigeminus was present intermittently. No periods of tachycardia were observed, and at times there were periods when the extrasystoles were infrequent. Quinidine sulfate was continued in the same dosage and the patient was placed on ammonium chloride and a mercurial diuretic. On May 22, 1944 extrasystoles were still present although less frequent, and two days later no extrasystoles were present. Quinidine sulfate was then omitted. At no time did the patient complain of nausea, visual or mental disturbances. Digitalis was again resumed but in reduced dosage, the patient receiving 0.1 gm. five days a week. On May 27, the patient was discharged much improved, having lost about 10 pounds of edema fluid.

## Discussion

There is little doubt that the ventricular tachycardia in this case resulted from an excess of digitalis since it developed only after the dosage of digitalis had been increased and subsided following the withdrawal of the drug. The patient did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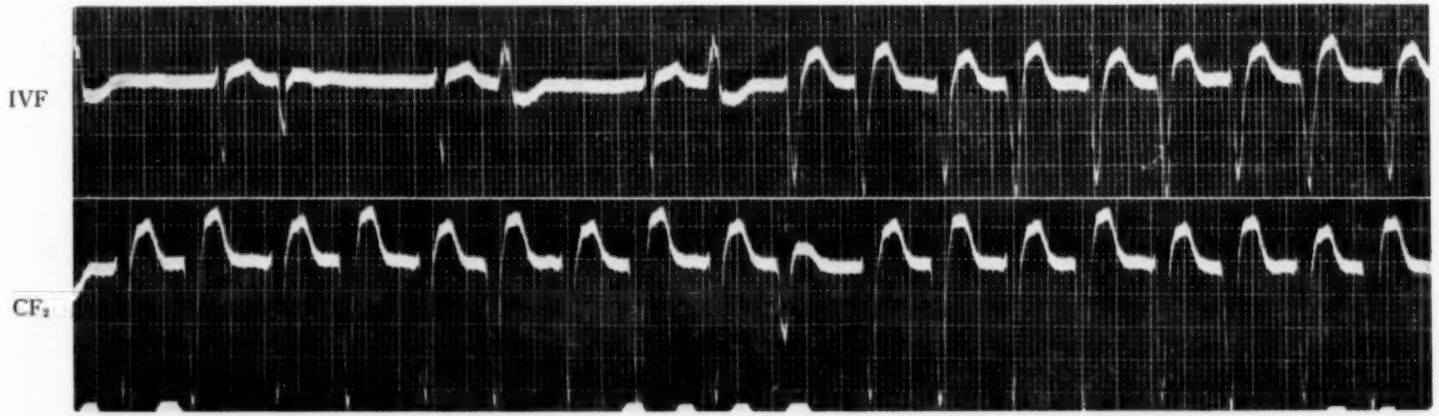


FIG. 1. The electrocardiogram taken on the day of entry to the hospital. Lead I demonstrates a tachycardia of 140 which is very slightly irregular and with alternation of the amplitude of the QRS complexes. The complexes are unidirectional and of equal duration (0.13 to 0.14 sec.). In Lead II, auricular fibrillation is present with fairly regular ventricular extrasystoles of two varieties and one short run of ventricular tachycardia of three complexes. In Lead III, the onset of ventricular tachycardia is seen with again the alternation in the amplitude of the complexes. In the two precordial leads, the usual type of ventricular tachycardia is seen with quite uniform contour of the ventricular complexes. The rhythm is slightly irregular. In Lead IV F, there are two types of ventricular extrasystoles as in Lead II before the onset of the ventricular tachycardia. A very slight electrical alternans is present in Leads IV F and $CF_2$ (1 to 2 mm.).

not, however, have any of the systemic symptoms of digitalis intoxication. The quinidine had a definite quieting effect upon the heart and reduced the duration and frequency of the paroxysms of ventricular tachycardia.

Although the QRS complexes in the electrocardiogram during ventricular tachycardia are usually fairly uniform, considerable variation of the complexes occurs in a few cases. When there is rhythmic variation of the complexes, it is most commonly an alternation in the direction of the ventricular complexes. The mechanism by which this odd type of pattern is produced is not clear. Palmer and White [3] listed five possible mechanisms: (1) alternating right and left bundle branch block; (2) alternating refractoriness of the large bundles of Purkinje fibers; (3) two separate foci; (4) reëntry phenomenon and (5) a double ventricular circus movement.

Rhythmic variation during ventricular tachycardia other than the bi-directional type is exceedingly rare. Only one other recorded electrocardiogram of the reported cases at all resembled the electrocardiogram in the case presented here, and that was an unusual case of a 21 year old boy reported by Scherf and Kisch.[5] The ventricular tachycardia did not result from digitalis intoxication in their case. The complexes were unidirectional and varied in amplitude, form and duration of diastole.

In Leads I and III of figure 1, the variation is of amplitude and form of the complexes although the duration of diastole and intraventricular conduction remains uniform. This gives the appearance of electrical alternans. The duration of diastole is uniform in this case during the tachycardia which is in favor of the paroxysmal tachycardia having a single focus of origin. The alternating variation in the QRS complexes would then be explained by imperfect conduction through the Purkinje conducting system on alternate systoles, possibly a result of conduction fatigue during alternate systoles. The several types of ventricular extrasystoles demonstrated in Lead II of figure 1 indicate a high degree of irritability of the ventricular musculature.

The phenomenon of electrical alternans has been compared recently with pulsus alternans and is considered a sign of serious myocardial disease.[6] No doubt the bizarre type of electrical alternans presented in this case is similar in its origin and clinical implications to that of electrical alternans occurring in cases with paroxysmal auricular tachycardia. Although this patient survived the ventricular tachycardia, she died three months later from congestive heart failure.

## Summary

A case is reported in which alternation in amplitude of the QRS complexes occurred in the electrocardiogram during paroxysmal ventricular tachycardia resulting from excess digitalis therapy. This phenomenon has been compared with the electrical alternans occurring at times during paroxysmal auricular tachycardia and is considered a sign of serious but not necessarily lethal heart disease.

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## TRAUMATIC RUPTURE OF THE AORTIC VALVE: REPORT OF TWO CASES, ONE A PROVED AND THE OTHER A PROBABLE EXAMPLE OF THIS CONDITION *

By BEN B. BUSHONG, M.D., F.A.C.P., *Traverse City, Michigan*

EXAMPLES of rupture of the aortic valve by trauma or strain have appeared sporadically in the literature since 1830, when Plenderleath [1] reported the first case in the London Medical Gazette. An excellent and comprehensive review of the subject was made in 1925 by Howard,[2] who set himself the thankless task of combing the literature from 1830 to 1925 for reports dealing with this rare condition. He succeeded in finding 112 cases, 49 of which were proved by autopsy. A search of the literature from 1925 to the present has yielded seven more cases, including that of Howard, making a total of 119 cases, 58 of which were proved by autopsy. The present report is of two additional cases, one proved by autopsy and one as yet unproved.

### CASE REPORT

*Case 1.* I. G., a 50 year old male truck driver, was perfectly well until two weeks prior to admission to University Hospital June 2, 1939, when a load of fence posts fell onto him in the cabin of a truck he was driving, striking a heavy blow against his back and right shoulder. While straining to extricate himself from beneath the posts, he experienced a sudden pain and tightness in his chest. He became short of breath and this continued, with severe paroxysms of dyspnea at night, up to the time of his admission. He was seen by Dr. Robert S. Ballmer of Midland, Michigan soon after the accident and the peculiar character of the physical signs was appreciated and the probable diagnosis was suspected by him. Digitalization had been completed and he was receiving aminophyllin 0.1 gm. three times daily before he came to the hospital.

The past history was not contributory. He had never been sick and denied venereal disease.

Physical examination revealed a well developed and nourished white male of 50 years in acute respiratory distress. The temperature was 98.6° F., the pulse 80 per minute, and respirations 24 per minute. The blood pressure was 175 mm. Hg systolic and 55 mm. diastolic. The pupils reacted normally to light. The ocular fundi showed some arterio-venous nicking and there was definite pulsation of the retinal arteries.

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From the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Michigan.

Chest expansion was free and equal on both sides, but resonance was impaired over both lung bases posteriorly. Fine, moist râles could be heard as high as the inferior borders of the scapulae. The heart was enlarged with the left border of cardiac dullness 13 cm. to the left of the mid-sternal line in the sixth interspace. The point of maximum impulse was lateral to the nipple and there was definite evidence of over-activity of the heart. A diastolic thrill could be felt in the aortic area, and in this region a loud, buzzing early diastolic murmur could be heard. It had a definitely

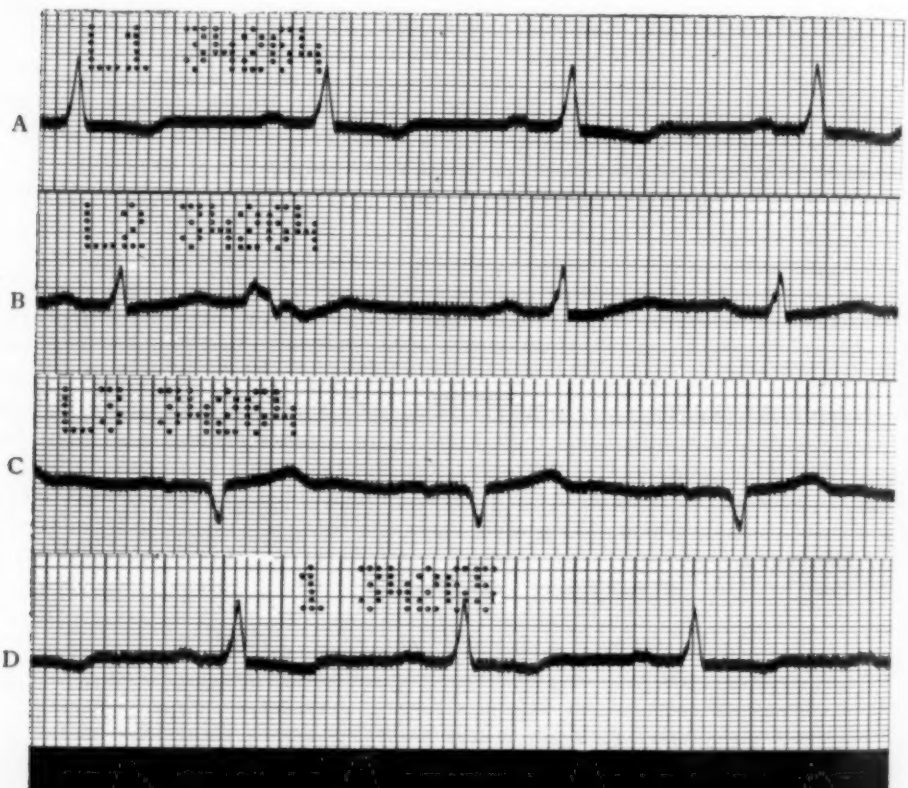


FIG. 1. Records from Case 1. A, B, and C show standard Leads I, II, and III. There is slight left axis deviation and inverted T-waves are present in Lead I. One ventricular premature beat is seen. D shows a sound tracing (below) taken over the upper sternum simultaneously with Lead I. The regular character of the oscillations indicates the musical character of the aortic diastolic murmur.

musical quality, could be heard over the entire precordium and much of the thorax, and was transmitted well into the neck vessels. Abdominal examination was unsatisfactory because the patient was unable to lie down. The liver was not felt and no masses were present. The extremities showed pitting edema of the feet and ankles. The nail-beds were cyanotic.

The blood Kahn test was negative. The hemoglobin was 89 per cent; the red blood count was 4,050,000 and the white blood count 9,000. These values, as well as

the differential counts varied, as might have been expected, during his hospital course. A series of chest roentgen-rays traced changes in the heart and lungs from admission until two days before his death. At no time were the lung fields free of congestion, and in the later films pulmonary consolidation of the right lower and middle lobes was seen, as well as a right pleural effusion. Electrocardiograms and sound tracings over the base of the heart were made and are shown in figure 1.

In spite of the usual treatment for congestive heart failure and complicating pulmonary infection, the patient failed to improve significantly and died on the fifty-fifth day of hospitalization approximately 69 days after the original trauma.

A summary of the relevant autopsy findings follows: The cardiac apex was 13 cm. to the left of the mid-sternal line at the level of the sixth interspace. The pericardium was slightly distended but showed no other abnormality. The heart was enlarged and weighed 650 grams. The apex was markedly broadened in comparison with the normal. Both ventricles and auricles showed hypertrophy and dilatation. The wall of the left ventricle measured 14 mm. in thickness. The endocardium was smooth and shiny throughout. The mitral valve was normal except for terminal dilatation. The aortic valve showed a transverse rupture, 1 cm. in length along the line of the insertion of the right anterior and posterior cusps and including the commissure, thus allowing the cusps to prolapse downward into the ventricle and the commissure to move away from the wall of the valve ring. The right ventricle showed dilatation but was not abnormal in other respects. The pulmonic and tricuspid valves were normal. The coronary ostia were normally located and showed only slight atherosclerosis.

*Case 2.* R. H., a boy of 11 years, was in good health until eight months prior to his visit to University Hospital on November 13, 1945, when his mother took him to a competent pediatrician because of a digestive upset. At this time no cardiac abnormality was found. Six months later his mother, who chanced to be sleeping with him, heard a peculiar noise in his chest. She took him to his doctor who detected a heart murmur. At this time the boy had no unusual dyspnea, chest pain, or other cardio-respiratory symptoms, but did state he would fatigue rather easily on moderate exertion. He gave no history of rheumatic fever or other serious illness in the past and was not a blue baby. On initial questioning no history of trauma was elicited. Later, however, the boy's father returned and volunteered the information that several months previously, while boxing with his son he had landed a solid blow on the boy's chest, which floored him and knocked the wind out of him. He complained of no pain or other symptoms, however, and shortly afterward seemed all right. There had been no other trauma.

Examination revealed a rather large male child of 11 years who appeared to be in good health. The blood pressure was 130 mm. Hg systolic and 20–0 mm. diastolic. There was rather marked systolic arterial pulsation in the supra-sternal notch and above the clavicles. The lungs were clear. The heart was moderately enlarged, with the left border of cardiac dullness just inside the left anterior axillary line. The heart rate was approximately 80 per minute, and there was no arrhythmia. A diastolic thrill was felt in the aortic area and down the left border of the sternum. In this region, a very loud, musical, early diastolic murmur was heard. No other murmurs were audible. The pulses were of the Corrigan type and Duroziez's sign was present.

Electrocardiograms and sound tracings taken over the base of the heart were made and are shown in figure 2.

## Discussion

As noted by previous writers, the majority of instances of rupture of aortic valves occur in valves that were previously diseased or abnormal. Plenderleath,[1]

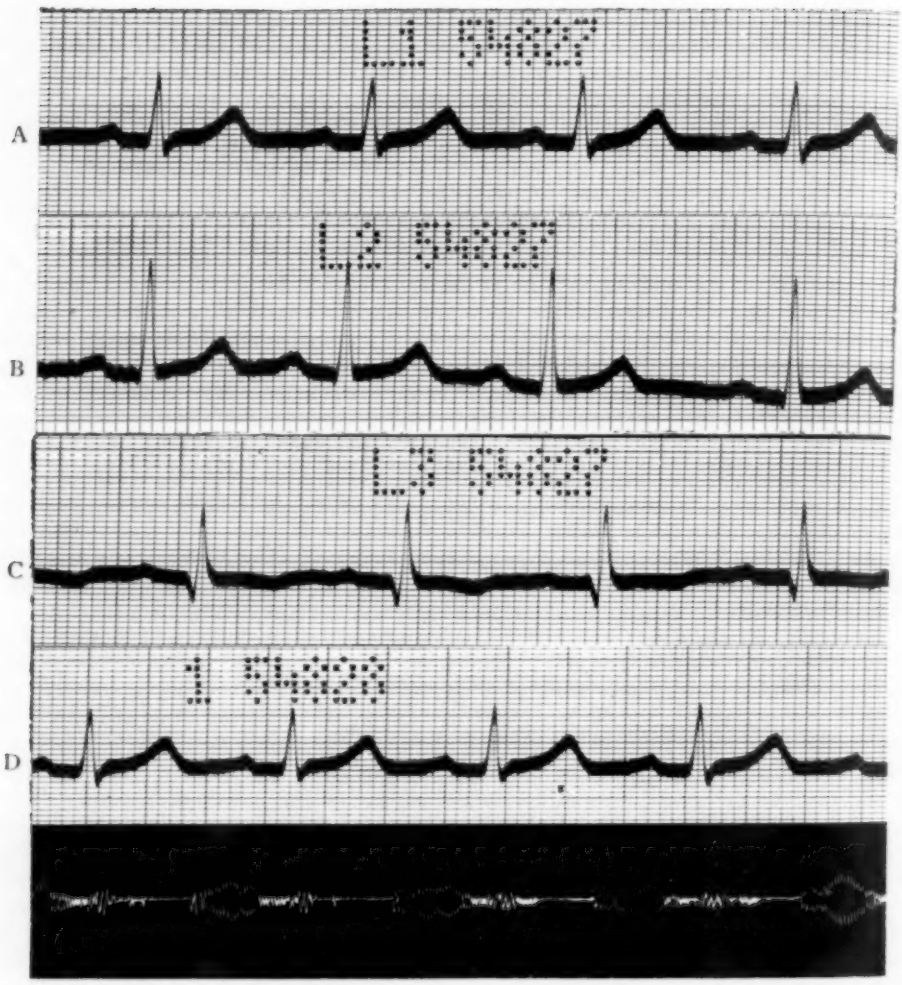


FIG. 2. Records from Case 2. A, B, and C, the standard leads, are well within normal limits. D shows a sound tracing taken over the upper sternum, simultaneously with Lead I. It indicates the musical character of the aortic diastolic murmur.

in reporting the first proved case in 1830, described the valves as "thickened red, and in the tendinous margin loaded with calcareous matter." Porter,[6] in 1931, had the unusual experience of hearing an aortic valve rupture as he was listening to the heart of a patient with acute gonococcal endocarditis. In this case, rupture was followed immediately by fatal edema of the lungs. A smaller number of cases have been reported of rupture of previously normal valves. The case reported by Kissane et al.[3] in 1936 was such an instance, the patient having been examined by the authors before the rupture occurred. Of the two cases here reported, the first was an instance of rupture of a normal valve. The valve in the second case had also been found normal in a previous examination, but the possibility of a congenital anomaly such as bicuspid valve cannot be excluded.

The presence of a very loud musical aortic diastolic murmur, particularly in individuals in whom trauma has occurred and previous examinations have revealed no murmur, should always suggest rupture or perforation of the aortic valve.

SUMMARY

Two cases of traumatic rupture of the aortic valve are presented. In one case, the antemortem diagnosis was confirmed by necropsy, whereas, in the second patient the history and the physical findings appear to justify a presumptive diagnosis of this condition.

The author wishes to express his appreciation to Dr. F. D. Johnston for help in the preparation of this paper.

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## DIAPHRAGMATIC SPASM ASSOCIATED WITH RECURRENT LEFT PNEUMOTHORAX *

By CHARLES H. SCHEIFLEY, Capt., M.C., *Rochester, Minnesota* and MILTON S. SASLAW, Lt. Col., M.C., A.U.S., *Miami, Florida*

As early as 1832 a report on "diaphragmatic convulsion" was described by Merat.[1] Since that time there have been a considerable number of cases of spasm of the diaphragm reported in the literature. None of these was verified by roentgenograms or fluoroscopy. In 1916, two cases were described by Simonin and Chavigny,[4] one associated with tuberculosis and the other following trauma of the chest. These were proved by fluoroscopy. Since that date a small number of cases have been described which were verified by fluoroscopic examination. Most of these were apparently sequelae of encephalitis.[8, 9, 11, 13, 15, 16, 17, 21] Other cases were attributed to surgical abdominal conditions,[17] such as intestinal obstruction with repeated laparotomies,[27] the presence of a cervical rib,[8] a fracture of the xiphoid process [12] and even pregnancy.[24]

* Received for publication August 28, 1945.

There is some confusion in the literature because of the use of various terms to describe diaphragmatic disturbances. The terms "convulsion," "tic," "spasm," "flutter," and "pleurodynia" have all been used. We suggest the term "spasm" be used with the modifier, "tonic" or "clonic" as indicated by the characteristics of the case. Its use in this way would be adequate for all instances except epidemic pleurodynia, which is a separate disease entity.

Spasm of the diaphragm as reported in most cases involved clonic contraction of one or both leaves of the diaphragm. In these cases the diaphragm contracted and relaxed at 100 or more times per minute and thus appeared to "flutter." These clonic spasms either disappeared spontaneously or finally required phrenic exeresis for relief.

Whitehead, Burnett, and Lagen [26] in 1939 described a case of "diaphragmatic flutter" with symptoms suggesting angina pectoris. In this case, pain was precordial and radiated down the left arm. It was severe, related to emotional stress and was diagnosed as hysterical. Phrenic nerve resection gave only temporary relief. On fluoroscopy, both leaves of the diaphragm were found to flutter at a rate of 200 vibrations per minute. No evidence of organic disease was found, and attacks recurred several times during a five year period.

In a case with intestinal obstruction, Handron [27] suggested that adhesions following repeated abdominal operations might be responsible for the diaphragmatic "tic." Following a fifth laparotomy for intestinal obstruction, his patient experienced severe pain in the left scapular area and left upper abdomen. It occurred in attacks which were sometimes precipitated by eating. Clonic spasm of the left diaphragm at the rate of 125 vibrations per minute was proved by fluoroscopy. Each attack was accompanied by hyperventilation, alkalosis and mild tetany. It was characteristically relieved by dilaudid and bilateral phrenic resection gave complete relief.

In a case described by Skillern [15, 21] of "tic" or clonic spasm of the diaphragm occurring after encephalitis, the patient experienced a fluttering sensation, but there was no pain. Repeated phrenic nerve interruptions resulted in each case in only temporary relief. Complete exeresis bilaterally was finally required for relief of the patient's symptoms.

Joannides [20] in 1935 described a case of acute primary diaphragmitis (Hedblom's syndrome). This is simply acute pain in the right abdomen occurring when the diaphragm is irritated by pneumonia or perforated ulcer. There is no spasm involved, however, except that commonly seen in protective splinting of the chest. Kulenkamp,[10] Roemheld,[18] and Lurje and Stern [14] described a slightly different condition in which diaphragmatic pain occurred as a result of pressure when the stomach was distended by air. This syndrome lacks the evidence of spasm or diaphragmatic dysfunction and hence is not related to the present discussion.

## Case Report

The patient was a 26 year old captain. His health had been excellent until January 1944 when he developed an acute upper respiratory infection with considerable coughing. The cough, largely non-productive, persisted throughout February and March. On March 17, while coughing he developed a severe pain in his left lower chest which radiated to the left shoulder. Roentgenologic examination revealed a left pneumothorax with about 10 per cent collapse. The lung promptly reëxpanded.

and the patient's cough disappeared. However, a dull aching pain in the lateral aspect of the left lower chest was noted which was persistent but did not interfere with his duties. While sitting at his desk on July 23, 1944, he experienced an acute pain similar but more severe than that occurring in March and associated with a sensation of breathlessness.

On admission to this hospital on August 24, 1944, the results of physical examination were entirely negative except for the usual signs of pneumothorax. Roentgen-ray revealed a partial left pneumothorax. Repeated sputum examinations including guinea-pig inoculation with gastric washings failed to reveal the presence of acid-fast organisms. The tuberculin test was negative. Blood counts and sedimentation rates were normal. The lung slowly reëxpanded, but the patient continued to have an aching pain in the left lower chest. Early in December 1944, this chest pain, which was present daily, became more severe and began to occur in acute attacks. It originated in the left lower antero-lateral portion of the chest and radiated over the crest of the left shoulder. It occurred spontaneously but was also noted whenever the patient coughed, breathed deeply, changed position or exercised. Exercise initiated sharp knife-like pain in this area which was best described as "spasms of pain" occurring 10 to 30 times per minute, making it difficult for the patient to breathe and so severe that opiates were needed for relief. These attacks awakened the patient from sleep. The characteristics of this pain and its precipitating factors were indistinguishable from those described as occurring in pleurodynia. The patient walked in a stooped position favoring the left side. There was no evidence of recurrence of the pneumothorax. Observation of the patient's thoracic wall during an episode of this pain revealed the presence of marked tonic contractions of the muscles of the left lower chest and left upper abdomen. Fluoroscopic examination while this pain was in progress visualized tonic spasms of the diaphragm which coincided with the severe episodes of pain.

A novocaine block of the left phrenic nerve was contemplated, and the patient was transferred to a hospital designated as a center for diseases of the chest. However the frequency and severity of the attacks subsided gradually and spontaneously, and this procedure was not carried out. By the end of a three-month period, the patient was symptom free.

## Comment

We have been unable to find any other case in the literature in which diaphragmatic tic has occurred as a sequel to pneumothorax, either spontaneous or induced. This is particularly unusual in view of the large number of cases in which artificial pneumothorax has been induced. The case we have described differs from other cases of "flutter" or "tic" since the spasm was tonic rather than clonic or "fluttering", and was associated with pain rather than the feeling of flutter. It may be that some of the reported cases were characterized by tonic contractions, but none was so described. The few cases of painful "tic" described all showed flutter fluoroscopically. On the other hand, all but a few of the cases of "flutter" reported were postencephalitic and were not associated with pain.

An interesting observation was the fact that position and exercise apparently played a trigger rôle in initiating attacks of diaphragmatic spasm and pain. Although this case cannot be described as one of epidemic pleurodynia, it is remarkable that the type of pain, its location, the postural factor and the precipitating factors were identical to those described for epidemic pleurodynia.[81] Likewise, all other cases of diaphragmatic dysfunction both with and without pain

have been associated with rapid clonic spasm or flutter instead of a *tonic* spasm as was noted in our case. In this respect it further mimicked epidemic pleurodynia.

## Summary

A case of *tonic* contraction of the diaphragm is described, presumably due to spontaneous pneumothorax, and various considerations in regard to various dysfunctions of the diaphragm are discussed.

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## ADRENALIN PRODUCING TUMOR (PHEOCHROMOCYTOMA) CONTAINING 2300 MG. OF ADRENALIN *

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PHEOCHROMOCYTOMA, the "physiologically malignant" [1] and histologically benign adrenal medullary tumor produces a clinical picture almost identical with that produced by large doses of epinephrine.

One hundred and fifty cases have been reported. The increasing frequency of antemortem diagnoses, particularly in the last decade has shown that the rarity of this clinical syndrome is more apparent than real. Because of the demonstrated effectiveness of the surgical treatment it is important that physicians be aware of this pathologic entity and the methods of assuring a correct diagnosis. Forty-one of the 150 cases have been treated surgically since the first operation by Charles Mayo in 1927.[2] Seventy-five per cent have been cured. Successful removal has been accomplished in patients ranging in age from 16 months to 65 years.[3, 4]

We report a case which we have studied comprehensively. We feel that it has several peculiarities which justify its report—viz., bilateral adrenal tumors, associated metastatic carcinoma of the thyroid, and the relatively simple confirmatory tests made to substantiate the clinical diagnosis.

The syndrome associated with pheochromocytoma is characterized mainly by acute unpredictable attacks lasting from a few seconds to several hours. In a typical attack there is sudden cardiac palpitation with either an increase or decrease in pulse rate (depending on the reflex mediated via the carotid sinus pressor mechanism) and a very marked rise in the blood pressure.[5] The patient notices a feeling of fullness in the throat and choking, and perhaps fullness, pressure, pain or burning beneath the sternum and in the epigastrium. There are often noted tingling and blanching of the extremities and tip of the nose together with pallor and generalized sweating. The pallor is followed by flushing. The patient characteristically feels nervous or anxious, tremulous and weak and has a headache, vertigo, blurred vision, mydriasis and perhaps tinnitus

* Received for publication April 30, 1946.
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and air hunger. Polyuria is common and gastrointestinal symptoms such as sialorrhea, nausea, vomiting, colic and diarrhea are not infrequent. Epiphora is often noted. Other objective manifestations are angiospasm in the ocular fundi, glycosuria, albuminuria and hyperglycemia. Unusual susceptibility to surgical shock and pulmonary edema are also characteristic.[6]

Cases have been reported in which hypermetabolism was the outstanding clinical finding.[7, 8]

## Case Report

A. M. M., a 39 year old white woman, married and without children, was admitted to the Indiana University Medical Center on October 24, 1944. Her only complaint was persistent profuse sweating.

She was born in Nebraska and had lived in the southern states most of her life. For the 10 years before admission she had been a laboratory technician in Federal laboratories, testing bovine and caprine blood for "Bang's disease."

The patient had severe chorea when she was 14 years old. At that time she was hospitalized for three months and was released following a tonsillectomy. She was in good health thereafter until 1938, when she developed weakness, palpitation, tachycardia, nervousness, and a tendency to fall over on stooping. A right hemithyroidectomy was done for relief of these symptoms. She remained well until 1942.

Early in 1942 a pain in the right lower quadrant led to a right oöphorectomy, salpingectomy and appendectomy.

In the summer of 1942 the attacks of profuse sweating began. These were so severe that her clothes often became saturated in a few minutes. The attacks at first were mild but they gradually increased in frequency and severity. She began to have a new form of attack. These new seizures were first noticed in the summer of 1943. She attached no importance or significance to these symptoms. They were often initiated by emotional strain—one followed the sudden return of a brother from the armed services—by pressure of work, carrying heavy objects, and sometimes there was no apparent cause. Rarely the attacks would awaken her. These attacks had no definite relationship to her profuse drenching sweats. She referred to these attacks as "the jitters." The typical "jitters" attack would begin with a dull, "cramping ache" and feeling of fullness in the pelvis and quickly radiated upward to the region of the costal borders. This was either accompanied or preceded by pain and tenderness in an enlarged lymph node located one inch below the mastoid. Nausea and non-projectile vomiting would follow. The vomiting in the severe attacks was attended by involuntary emptying of the bladder. Her scalp would "tingle" as though the hair was standing on end. She would become "jittery and shaky." Tachycardia, extremely active precordium, dyspnea, and orthopnea occurred a few minutes after the vomiting ceased. Her attitude was one of extreme fright. She had a noticeable exophthalmos and scleral injection. Vision would become blurred and the patient complained of a twitching sensation in her eyes. Her face would take on a waxen pallor and mottled appearance. Circumoral pallor and cyanosis of the lips were present at the height of the attacks. After "the jitters" were over she was completely exhausted and very warm. The attacks lasted several minutes to several hours. On no occasion prior to this hospital admission was her blood pressure taken during an attack. Her local physician told her previously that she had a mild hypertension.

In November 1943, the patient suffered pain in the left loin. Medical consultants made a diagnosis of kidney disease and the patient was given sulfonamide therapy for a period of three days. A remission of symptoms followed.

She had no other illnesses of importance. Blood pressure taken by one of us before hospital admission was 174 mm. Hg systolic and 100 mm. diastolic.

*Physical Examination.* The patient was healthy in appearance and looked younger than her stated age. She was well developed and well nourished and was sweating profusely. She was calm and deliberate throughout her entire examination. Weight was 105 pounds (47.7 kg.), height 4 feet, 11½ inches, temperature 99° F., pulse rate 95, respirations 16 per minute and blood pressure 164 mm. Hg systolic and 110 mm. diastolic. The skin surfaces revealed many scattered sudaminia and mild eczematous areas in the regions which were most moist. Hair distribution over the body was of the normal female type. The temporal and radial vessels were normal. Perspiration extended well back into the scalp, and the hair was moist and oily. The eyes reacted well to light and accommodation. Extra-ocular movements were normal; pupils small, round and equal. No noticeable exophthalmos was present. Ophthalmoscopic examination was entirely normal with the exception of slight tortuosity of the arteries of the fundus oculi. There was no visible sclerosis and no evidence of any hemorrhages. The neck showed no extraordinary pulsations. A firm, enlarged node was found one inch below the mastoid bone on the right. A transverse thyroidectomy scar was present. The heart was not enlarged. A well transmitted, soft systolic blowing murmur was heard over the base of the heart. The abdomen was normal with the exception of a mass, firm and somewhat tender, high in the upper right quadrant. The mass was easily demonstrated on deep palpation when the patient took a deep inspiration. Reflexes were normal. Neurological, pelvic and rectal examinations were without abnormal findings.

There was nothing significant in the family history.

*Laboratory Examination.* Hemoglobin 13.0 gm., red blood cells 4.6, white blood cells 7,750 with a normal differential count. Bleeding time 2 minutes; coagulation time 1 minute, 25 sec. Urinalysis revealed a sp. gr. of 1.010 to 1.021. No albumin and no sugar were present. Blood sedimentation rate was 25; hematocrit was 50.5 per cent vol. packed cells. Mazzini flocculation test was negative. There were no agglutinations for *E. typhosus,* O and H antigen, para-typhosus, A and B antigen, and *Brucella abortus* antigens. Blood chemical studies revealed non-protein nitrogen 36 mg. per cent; fasting blood sugar was 83 mg. per cent; serum cholesterol was 343 mg. per cent and cholesterol esters 242 mg. per cent (Bloor method). Serum chloride (NaCl) was 631 mg. per cent. Serum protein was 7.10 mg. per cent; serum albumin 5.68 gm. per cent and serum globulin 1.42 gm. per cent. Twenty-four hour urine specimen sodium chloride was 700 mg. per cent, chlorine 420 mg. per cent. An oral glucose tolerance test revealed a fasting blood sugar of 107 mg. per cent with a negative urine sugar. One-half hour after ingestion of 100 gm. of glucose, the blood sugar was 164 mg. per cent. One hour following ingestion the blood sugar was 200 mg. per cent with 0.8 per cent urine sugar. Two hours after beginning the test, blood sugar had dropped to 138 mg. per cent and the urine showed 1.6 per cent sugar. Phenolsulphonephthalein test revealed 27 per cent excretion in 15 minutes and 39 per cent excretion in 30 minutes. Urea clearance test was 71 per cent of normal. Blood urea nitrogen per 100 c.c. was 17.6 mg. Urea index was 56. Serum sodium chloride was 620 mg. per cent. Basal metabolic rate varied from + 56 to + 74 on three separate days.

Once the diagnosis of pheochromocytoma is suspected from clinical manifestations, special diagnostic procedures are necessary for proving or disproving it and also for localizing the tumor if one be present. The procedures which we present here are for the most part simple enough to be carried out as office procedures if the proper precautions are taken to prevent the artificially induced attacks from reaching a maximum.

Perirenal pneumograms have been done in a large series of cases but are not

without danger and should be avoided by those having limited experience with this technic.[9]

Radiographic evidence corroborated our physical findings of a mass in the right hypogastrium.

*Roentgen-Ray Examinations.* "The depression of the superior calyx of the right kidney together with a suggestion of a mass overlying the superior pole of this kidney supports the possibility of there being a tumor of the right adrenal gland. The roentgen-ray studies of the skull show findings which appear to be within normal limits. Chest roentgen-ray is normal."

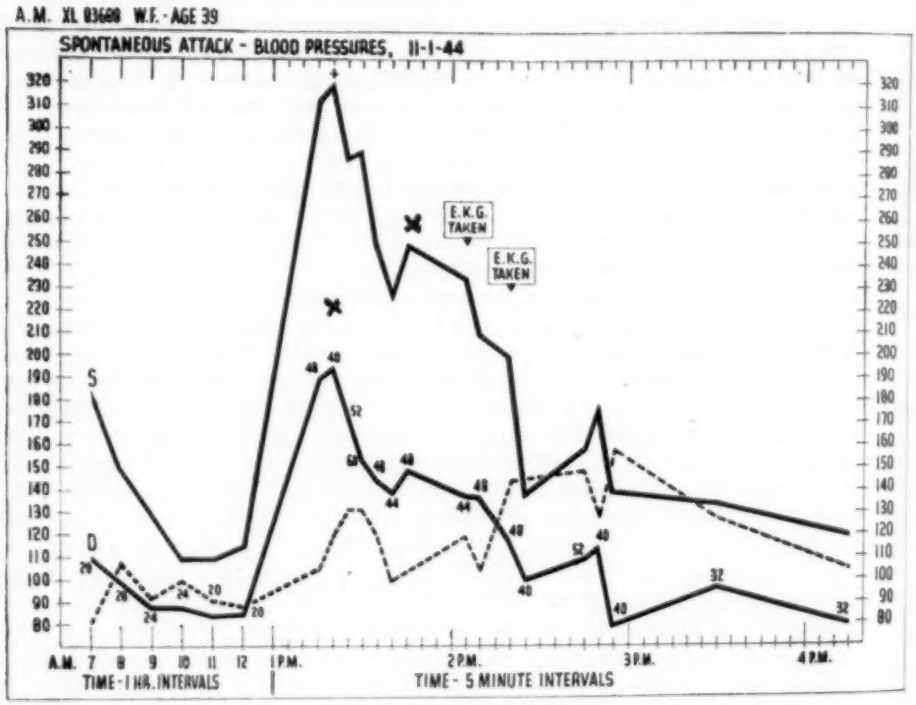


FIG. 1. Spontaneous Attack.
S = Systolic blood pressure.
D = Diastolic blood pressure.
The broken line represents the pulse rate.
Arabic numerals along line D = respirations per min.
Note time intervals.

*Typical Spontaneous Attack* (Figure 1). The onset followed the noon meal by one hour and came after four normal hourly blood pressure readings. The patient was lying on her back in bed when she was suddenly struck by a "twisting pain in the lump in the right side of the neck" (lump = lymph node one inch below mastoid process). At the same time a "lump" which started at the symphysis pubis moved up the midline to the costal margin. Nausea with vomiting of undigested food and involuntary emptying of the bladder lasted for about minutes.

Eyes: There was scleral injection, exophthalmos and a subjective complaint of "twitching feeling in back of eyes." There was circumoral pallor, a cyanotic tinge to the lips, and general waxen pallor especially noticeable over the face. The patient

also complained of a "drawing feeling" over the scalp. She then had profuse sweating, generalized except for the lower extremities. The knees had a mottled purple hue. She remarked that "legs ache, and hands and arms have a tingling feeling like an electric shock, and goose pimples all over." Weakness and exhaustion followed the fall in blood pressure. Dyspnea was common throughout. There was orthopnea during the vomiting attack. Severe coughing followed the onset by one and one-half hours. Subjective complaints lasted only 20 minutes after the onset. Blood pressure had returned to base line in two and one-half hours.

During this attack gr. 1/150 nitroglycerine (sublingual) was used twice in an attempt to abort the alarming pressure of 320 mm. Hg systolic and 195 mm. diastolic. (Pressure above 320 could not be recorded because of the limitations of the manometers available.) Nitroglycerine administered at "×" in figure 1.

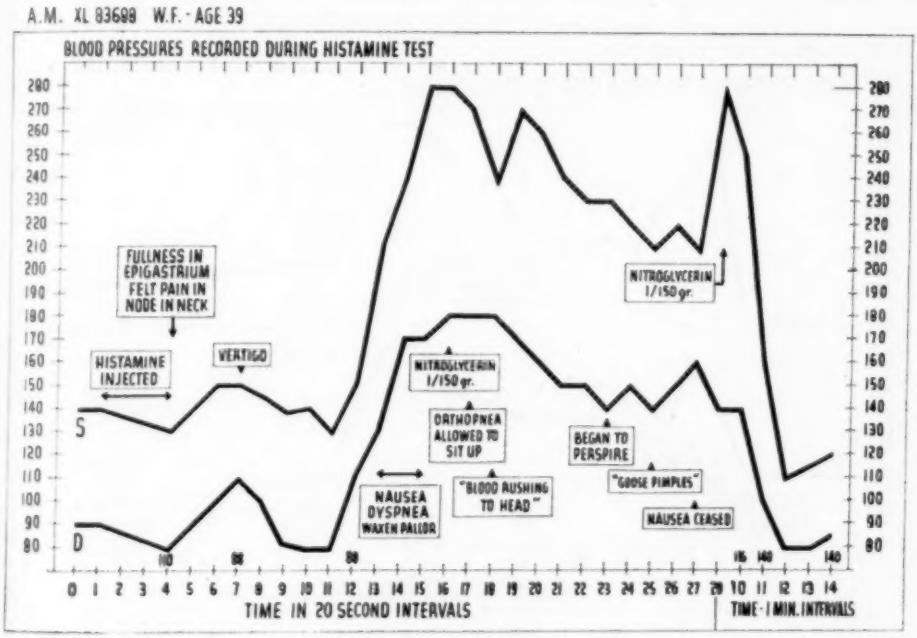


FIG. 2. Histamine Induced Attack.
Time intervals 20 seconds.
D = Diastolic blood pressure.
S = Systolic blood pressure.

An electrocardiogram taken approximately one hour after onset of the attack showed the P-wave peaked in $L_1$ and $L_2$, inverted in $L_3$. $T_1$ was diphasic but upright in $L_2$, $L_3$ and $L_4$. Left axis deviation was more marked than during normal periods. Rate was 150. Normal sinus rhythm and normal conduction times were present.

Oscillometric readings varied between 0–.5. Normal readings on this patient 1–1.5 in same region over calf muscles.

Repeated trials to induce an attack by changes in position failed.

Adrenalin was not used in an attempt to produce an attack because of the severity of the symptoms.

*Histamine Induced Attack* (Figure 2). Personal communication by one of us (J. O. R.) with Dr. Grace M. Roth and a case report from the Mayo Clinic led to the

use of a very simple test which Dr. Roth has devised for the study of epinephrine producing tumors. The pharmacological and physiological aspects of this are not clearly understood.[10, 11]

One cubic centimeter of histamine acid phosphate containing .025 mg./cu. cm. was used as test material. One-tenth of this material was injected I.V. No untoward reaction was noted after 30 seconds, and the remainder was then introduced by the intravenous route. (See figure 2 for graphic representations.)

The blood pressure fell slightly and then began a gradual rise to slightly above the average base-line . . . again there was a slight fall to the base line which was immediately followed by a very sudden and alarming rise to 280 mm. Hg systolic and 180 mm. diastolic. This took place four minutes after histamine introduction. Blood pressure was taken every 20 seconds throughout the experiment. The patient complained of vertigo, fullness in the epigastrium, and pain in the node in the neck before any rise in blood pressure was noted.

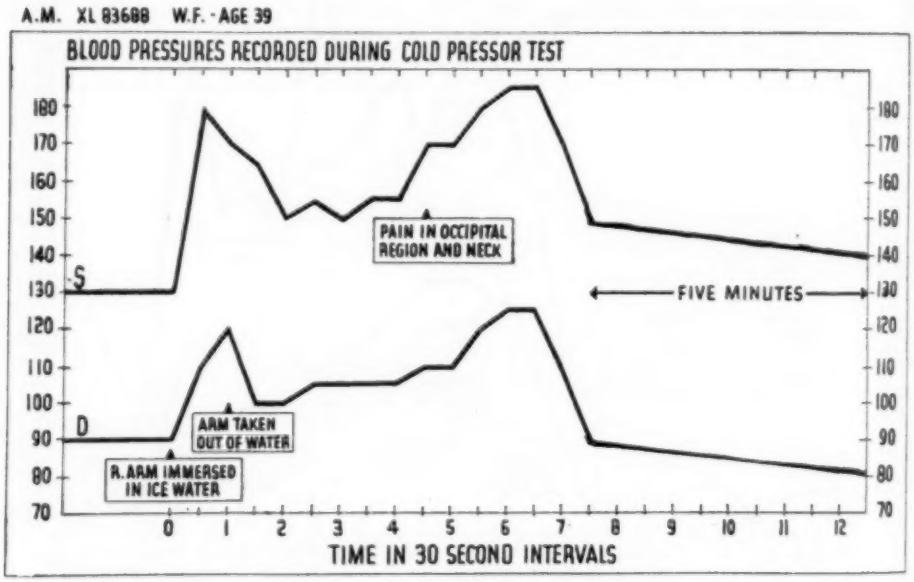


FIG. 3. The Cold Pressor Test.
S = Systolic blood pressure.
D = Diastolic blood pressure.

As soon as the blood pressure reached 280 mm. Hg systolic and 180 mm. diastolic the patient was given nitroglycerine 1/150 gr. She complained of severe dyspnea, nausea, "blood rushing to head," orthopnea and "cold." Her eyes had a terrified look. Exophthalmos was noted. Scleral injection was present. Dilatation of pupils was not noted. There was a circum-oral pallor, cyanosis of the lips and "splotched" appearance of the skin over the face and knees. The skin was cool and soon became covered with "goose pimples." The patient said that she could feel her hair standing on end. Approximately two minutes after sublingual administration of nitroglycerine the blood pressure began to fall but took another sharp rise in the next minute. The rise was again aborted with nitroglycerine. Blood pressure returned to base-line two minutes later, i.e., 12 to 13 minutes after administration of the test solution.

*The Cold Pressor Test* (Figure 3). The blood pressure prior to this test showed an average level of 130 mm. Hg systolic and 90 mm. diastolic. The sphygmomano-

meter was applied to one arm and the other arm was immersed in ice water. In 30 seconds the blood pressure had risen to 180 mm. Hg systolic and 120 mm. diastolic. The arm was removed from the ice water in 60 seconds and the pressure began to return to a normal level. In 3½ minutes a secondary rise began. It reached a peak of 185 mm. Hg systolic and 120 mm. diastolic, six minutes after the experiment was begun, and remained at this peak for 1 minute then returned to normal two minutes later.

*Massage over Tumor Area* (Figure 4). Active and passive changes of the patient's position had been unsuccessful in precipitating attacks. In an attempt to produce an attack the mass overlying the upper pole of the kidney was massaged vigorously for 10 to 15 seconds.

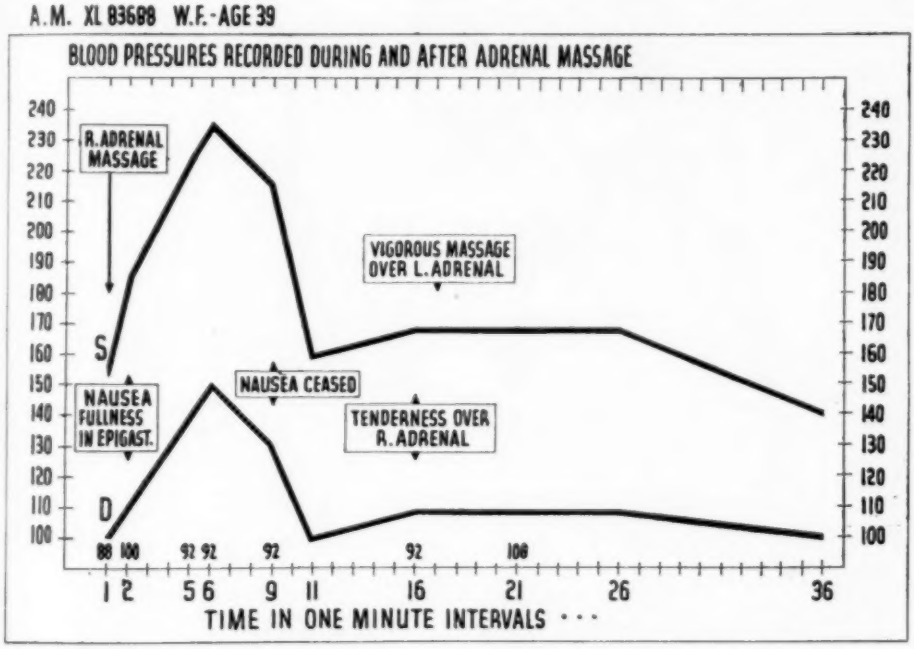


FIG. 4. Blood Pressures Recorded during and after Massage over Adrenal Areas.
Time interval 1 minute.
D = Diastolic blood pressure.
S = Systolic blood pressure.

Before this procedure the blood pressure was 155 mm. Hg systolic and 100 mm. diastolic (pulse 88) and immediately afterwards the blood pressure was 185 mm. Hg systolic and 110 mm. diastolic (pulse 100) continuing to rise until it reached a peak of 235 mm. Hg systolic and 150 mm. diastolic in five minutes.

After the massage over the mass, the patient calmly complained of being sick at her stomach and then experienced sensations identical with the spontaneous attacks. The patient also complained of tenderness in the upper right quadrant.

When the base-line pressure was obtained (16 min.) the identical area in the left upper quadrant was manipulated in the same manner without any change in the blood pressure.

*Sweating Test* (Figure 5). Figure 5 outlines the areas of perspiration (in their relative amounts and location). The areas were of interest because before fluctuations

in blood pressure were recognized the possibility of some sympathetic nervous system involvement such as caused by mediastinal tumors had to be ruled out.

The test of sweating areas and outline of these areas were done by Minor's method.[12]

Minor's test, in short, gave us the outline of the sweating areas which were bilaterally symmetrical and most noticeable in the fold areas.

*Surgery* (Figure 6). After the diagnosis was established and the necessary clinical laboratory studies were complete, pre-operative preparation was begun. The patient received one-half grain phenobarbital every four hours for four days prior to the day of operation. This proved sufficient to prevent any severe spontaneous at-

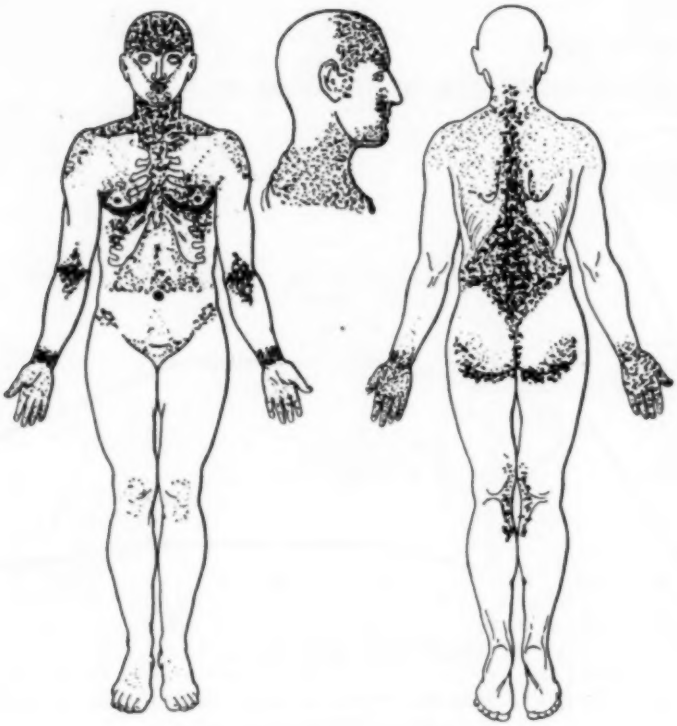

FIG. 5. Sweating Test, Minor's Method.

tack due to emotional upset. Two days before operation the patient was given hourly 15 gr. doses of sodium chloride in view of the post-operative adrenal cortical insufficiency which might have resulted.

Adequate preparation was made for any emergency which might have arisen during the surgical removal of the tumor. A vein was cannulated and a very slow drip rate established in order that drugs might be administered instantaneously if necessary.

The patient had gr. 1/150 atropine sulfate and avertin as pre-general anesthetic medication in her room. She was asleep when taken to the operating room. Her blood pressure was 140 mm. Hg systolic and 95 mm. diastolic. Nitrous oxide-ether anesthesia was then begun. Preoperative diagnosis was: Pheochromocytoma of the right adrenal gland.

At no time during the operation for removal of the tumor did the blood pressure

approach the height reached during some of the spontaneous attacks—the peak being 225 mm. Hg systolic and 130 mm. diastolic.

Incision: High right rectus. Peritoneum and transverse aponeurosis muscle opened diagonally from upper portion of wound downward and outward. The blood pressure began to take a gradual upward swing at this point.

Exploration: Numerous band-like adhesions connected the upper surface of the liver with the under surface of the diaphragm. These had to be freed. Blood pressure readings had by this time leveled off to 220 mm. Hg systolic and 145 mm. diastolic. Palpation of the tumor over the right adrenal area was then accomplished by the operator. Palpation of it was very gentle but immediately caused slight rise in blood

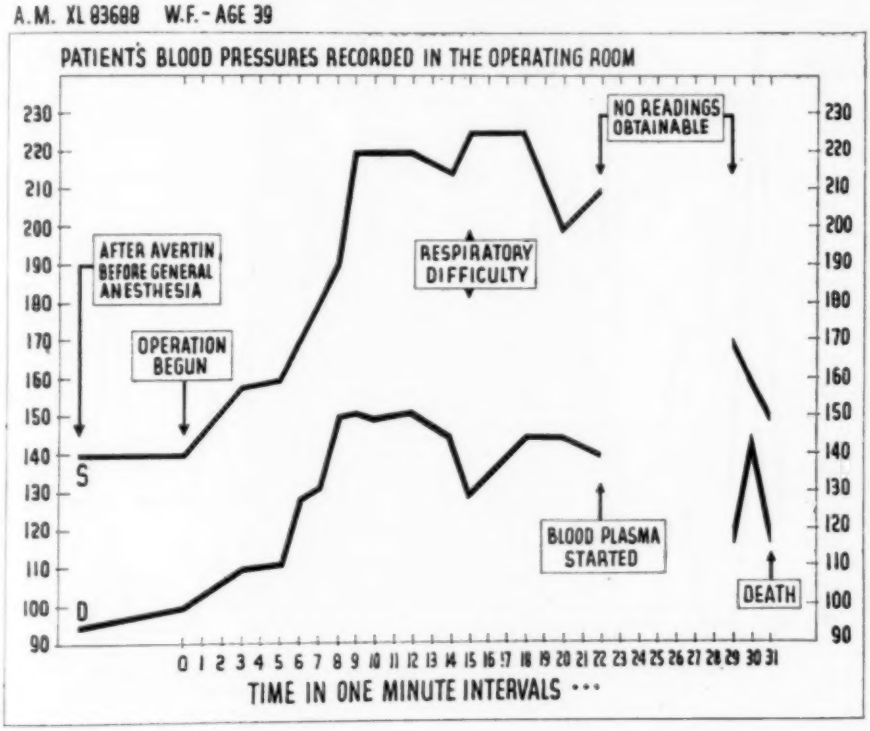


FIG. 6. Blood Pressure during Operation for Removal of the Tumor.
S = Systolic blood pressure.
D = Diastolic blood pressure.

pressure and respiratory difficulty. The operation was then discontinued for a time. The blood pressure came down and the condition of the patient seemed good. The liver was now retracted to the left and an attempt was made to separate the peritoneum along the line where it passed from the tumor to the under surface of the diaphragm. At this point the patient collapsed. During the collapse the wound was rapidly closed. The patient's condition and the size and location of the tumor warranted discontinuance of the operation and plans for a different approach after recovery. Her color was an ashen gray and great quantities of clear fluid poured from her nose and mouth. Although no blood pressure, pulse, or respirations were obtainable for a period of seven minutes, readings were again obtained and the blood pressure was 170 mm. Hg systolic

and 110 mm. diastolic . . . it began to fall again gradually and after four minutes the patient died despite every effort to save her.

Permission was obtained to remove the tumor. This was done through the original incision with most surprising ease. It was about the size of a medium orange, completely encapsulated, and seemed to have very few blood vessels attached to it.

The entire tumor weighed 350 grams. Part of the tumor was removed for microscopic study. The remainder was immediately packed in ice and sent to Dr.

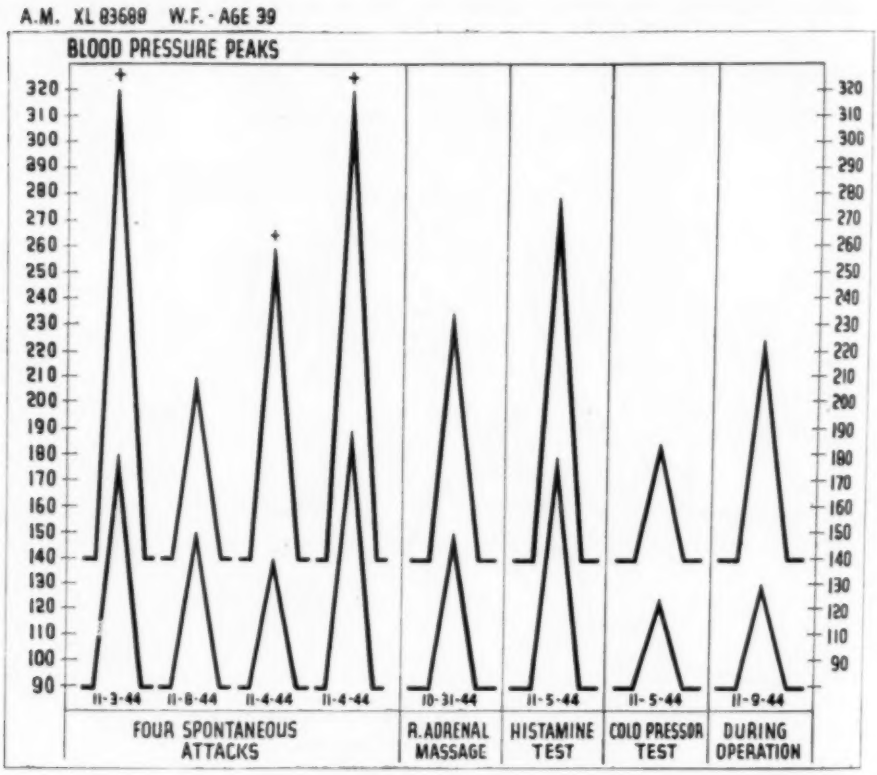


FIG. 7. Composite picture—blood pressure during various procedures. Four spontaneous attacks, the most severe of which resulted in a recordable blood pressure of 320 mm. Hg systolic and 180 mm. diastolic. Normal average base-line 140 mm. Hg systolic and 90 mm. diastolic. Right adrenal massage, 235 mm. Hg systolic and 145 mm. diastolic. The histamine test resulted in a peak pressure of 275 mm. Hg systolic and 175 mm. diastolic, but this attack was aborted by the use of nitroglycerine. The blood pressure rose to 185 mm. Hg systolic and 120 mm. diastolic during the "cold-pressor test."

K. K. Chen (Lilly Research Laboratory, Indianapolis, Indiana) who made an extract of the remaining 286 grams. This was made according to the method of Folin, Cannon, and Denis (Jr. Biol. Chem., 1912–13, xiii, 477), and a total volume of 12 liters was obtained (figure 8).

By a colorimetric comparison with a standard adrenalin solution, it was shown that the extract was 1.43 times as strong as a 1:10,000 adrenalin solution, volume for volume. The extract was then assayed by the blood pressure method of Elliott (Jr. Physiol., 1912, xliv, 374). It was shown that the extract by this procedure was 1.6

times as potent as a 1 : 10,000 adrenalin solution. An example of such a test is shown above. When calculated on the basis of the blood pressure method, the total amount of adrenalin present in 286 grams would be 1.92 grams, or 671 mg./100 gm. of the tumor.

Calculating then from the total weight, the amount of adrenalin in the whole tumor would then be 2.3496 grams. If we further calculate that a pair of beef adrenals, assayed biologically (Folin, Cannon, and Denis, Jr. Biol. Chem., 1912–13,

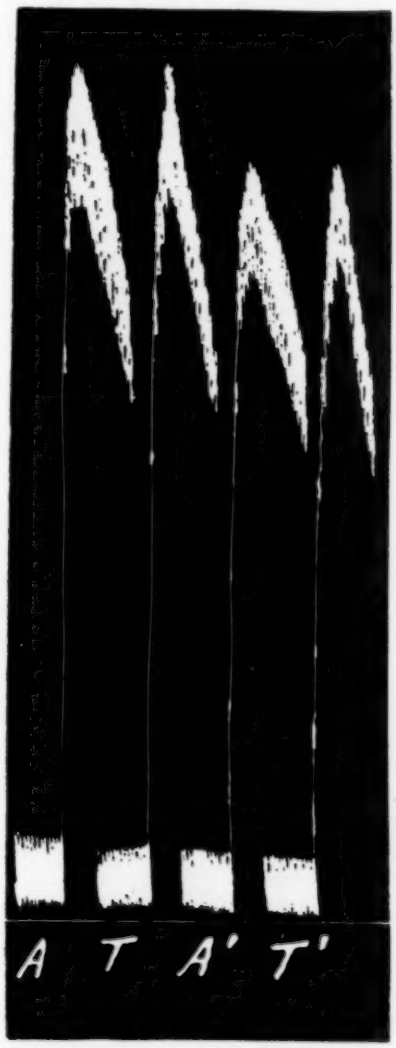


FIG. 8. Assay of the Adrenalin Content by the Blood Pressure Method

Dog, male, weighing 8.6 kg., was decerebrated and pithed—under artificial respiration. Both vagi were cut. The blood pressure responses were caused by the following solutions intravenously injected:

A —Adrenalin Solution, 1 : 10,000,0.2 c.c.
T —Tumor Extract, 0.125 c.c.
A'—Adrenalin Solution, 1 : 10,000,0.16 c.c.
T'—Tumor Extract, 0.10 c.c.

xiii, 477), contains 75 mg. of adrenalin, it will then take a herd of 31 cattle to give rise to the same amount of adrenalin that was present in this tumor.

Since an adult man has a maximum of 1 mg. of adrenalin in his adrenal glands (Elliott, Proc., Jr. Physiol., 1913, xlvi, xv), it would then take a company of 261 human subjects to give up the same amount of adrenalin as in our specimen.

Many of the tumors are cystic in nature and assay of a small piece of such a tumor would give misleading information as to the total amount of adrenalin in the tissue. We believe that the tumor is one of the very few that was assayed in its entirety, i.e., with exception of the small portion removed for pathological study and tissue section.

## Résumé of Postmortem Data

(From protocol prepared by Department of Pathology) by Dr. F. Forry and Dr. A. Michael

There was a bilateral cervical lymphadenopathy. An easily palpable firm node was found some 3 cm. below the mastoid process on the right. The lung showed the features of a typical pulmonary edema. The paratracheal nodes were moderately enlarged. Examination of the tissues along each of the carotid sheaths revealed several normal appearing lymph nodes. No structures were identified grossly or histologically as carotid bodies. The left lobe of the thyroid measured 2 by 1½ by 2 cm. and was rather firmly attached to the surrounding tissue. Attached to the capsule were two small nodules grossly resembling parathyroid. These measured 2 by 3 by 4 mm. Microscopic sections of thyroid show normal appearing thyroid tissue within which lies a partially encapsulated area of neoplastic tissue. The neoplastic tissue appears in alveolar masses or small clumps of cells surrounded by a dense fibrous connective tissue stroma. The neoplastic cells are epithelial in type. They varied from 12 to 18 micra in diameter. The nuclei tend towards pyknosis. In some fields the stroma exceeds the neoplastic tissue. Strands of neoplastic cells are seen growing in lymphatic channels. Several of the lymph nodes of the cervical and paratracheal chains show masses of neoplastic tissue, morphologically the same as that in the thyroid.

The dorsal aorta showed very mild arteriosclerosis. Search was made for the aortic body but this was not identified grossly or microscopically.

Examination of the loose tissues about the site of the tumor of the right adrenal revealed no evidence of infiltration by neoplastic tissue. The stump of the right suprarenal vein was normal grossly and histologically. The left suprarenal weighed 13.5 grams. It contained two spherical nodules apparently developing in the medulla. Each was about a centimeter in diameter. The left suprarenal vein showed no evidence of invasion by neoplastic tissue.

The remaining gross findings have no significant bearing in this case.

The outstanding and striking clinical manifestations recorded in the clinical notes were shown to be due to a large pheochromocytoma originating in the right suprarenal gland.

Several microscopic sections of the adipose and connective tissues about the right suprarenal tumor and of tissues at its hilus showed no evidence of extension of neoplastic cells beyond the confines of the tumor (figure 9).

Microscopic study of the two 1 cm. nodules present in the left suprarenal shows the histological picture characteristic for pheochromocytoma. In sections fixed in Zenker's solution, some of the cells in each of these two tumors are seen to contain fine yellowish brown granules. Repeated transverse sections through the left suprarenal and its two neoplastic nodules and its hilus likewise did not reveal histologic

evidence of extension into blood channels, along lymphatics, or into connective tissues. Although the contact zone between each of the neoplastic nodules and surrounding suprarenal tissue was irregular, none of the sections showed tumor cells wandering away from the parent tumor mass. Demonstration of a positive "chromaffin reaction" leads to the conclusion that these masses are pheochromocytomas of independent or multi-centric origin. No lymph node neoplastic disease was found below the diaphragm or lower mediastinum. The lymph nodes affected by neoplastic disease were all situated in the right and left anterior cervical chain and paratracheal nodes. These contained masses of neoplastic epithelium histologically like that found in the left

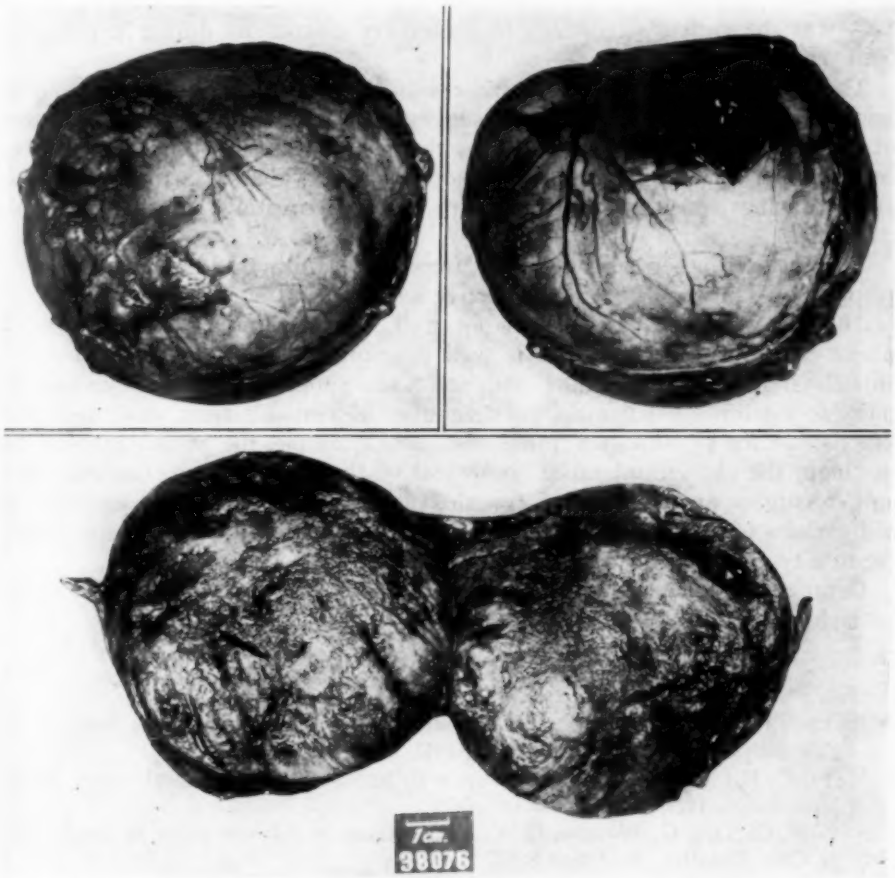


FIG. 9. Adrenal Tumor. Pheochromocytoma weighing 350 gm. and containing 2349 mg. epinephrine.

lobe of the thyroid. Sections through these nodes, the thyroid and adjacent tissue revealed numerous instances of lymphatic permeation. The neoplastic tissue in these nodes is histologically identical with that found in the thyroid. It does not resemble the tissue of the suprarenal neoplasms.

Anatomical Diagnoses: pheochromocytoma, right suprarenal; pheochromocytomas, left suprarenal; carcinoma, left lobe of thyroid; metastatic carcinoma (from thyroid) in cervical and paratracheal lymph nodes; pulmonary congestion and edema, bilateral.

Tissue sections made from the thyroid gland removed in a Des Moines hospital in 1938, were obtained recently. They show histological features identical with those of the neoplastic tissue found in the remaining thyroid tissue.

## Summary and Conclusions

The above represents a case report of pheochromocytoma, classical in all respects. In addition, there were the two tumors of like histological structure in the opposite adrenal. There was present an unrelated neoplasm, carcinoma of the thyroid with metastases to a cervical and the mediastinal lymph nodes. Of interest was the patient's tendency to center her discomfort during a paroxysm about the cervical node.

The patient uniformly showed the results anticipated in the various physiological tests. The histamine test as suggested by Roth and Kvale was as clear cut in our case as in those described by them. As was shown by them further, the histamine test was quantitatively more excitatory than was the cold pressor test producing a rise in blood pressure of approximately 100 mm. after the latter test.

As is true in other cases reported, ours had hemithyroidectomy for relief of symptoms. This was in a way effective subjectively for four years, though it was obvious that the patient was not well. The extreme lability of such a patient in a surgical procedure is well exemplified. Although the picture is quite classical and clear in most cases and a few simple observations will usually suffice to establish a diagnosis, yet a number of available tests more accurately demonstrate the physiological processes. For example, the basal metabolic rate was high, the glucose tolerance curve was of the diabetic type, the cholesterol high, roentgen-ray examination revealed depression of the kidney calices, the cold pressor test showed a marked response and massage over the tumor gave rise to a typical paroxysm as did the histamine test.

Complete detailed laboratory, clinical, physiological and pathological studies are included in the above report.

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6. Belt, A. E., and Powell, T. O.: Clinical manifestations of chromaffin cell tumors arising from the suprarenal medulla, Surg., Gynec. and Obst., 1934, lix, 9–24.
7. Kirschbaum, J. D., and Balkin, R. B.: Pheochromocytoma with hypermetabolism, Ann. Surg., 1942, cxvi, 54–60.
8. McCullagh, E. P., and Engel, W. J.: Pheochromocytoma with hypermetabolism, Ann. Surg., 1942, cxvi, 61–75.

9. HYMAN, A., and MENCHER, W. H.: Pheochromocytoma of the adrenal gland, Jr. Urol., 1943, xlix, 755.
10. KVALE, W. F., ROTH, G. M., CLAGETT, O. T., and DOCKERTY, M. B.: Headache and paroxysmal hypertension: observations before and after the surgical removal of a pheochromocytoma, Surg. Clin. N. Am., 1944, 922.
11. ROTH, G. M., and KVALE, W. F.: A tentative test for pheochromocytoma, Am. Jr. Med. Sci., 1945, ccx, 653.
12. LIST, C. F., and PEET, M. M.: Sweat secretion in man, Arch. Neurol. and Psychiat., 1938, xxxix, 1228–1237.

# EDITORIAL

## *PENICILLIN IN THE TREATMENT OF SYPHILIS*

LIKE many another new form of therapy, the penicillin treatment of syphilis has progressed through the cycle of dubiety, enthusiasm and reaction. Mahoney's original report [1] that penicillin is effectual against *T. pallidum* was received with some caution, but as laboratory and clinical confirmation of this observation rapidly became available, reserve quickly gave way to enthusiasm. So promising did this new form of therapy appear that in September 1943, within three months of the first public announcement, a nationwide cooperative study was organized under the auspices of the Committee on Medical Research. In less than a year penicillin was adopted for routine use in early syphilis by the United States Army. Since then the limitations of this form of therapy gradually have become apparent.

Even the most skeptical observer no longer denies that penicillin is a valuable adjunct to syphilotherapy, nor that it is, in some respects, superior to any previous form of treatment. That it has serious drawbacks is recognized by its most ardent protagonists.

The principal advantages of penicillin in the treatment of syphilis are its lack of toxicity, and the fact that the therapeutic schedule need not be inordinately prolonged. Consequently, the full course of treatment is almost invariably completed. This is not the case with any form of arsenotherapy, where toxic reactions increase in frequency the more the total duration of treatment is compressed, and where case-holding becomes increasingly difficult as the time period of therapy is prolonged.

The principal disadvantages of penicillin therapy are the probable essentiality of hospitalization, when the drug is given in aqueous solution, and the significant number of treatment failures (relapse and seroresistance in early syphilis, submaximal improvement in certain forms of late syphilis).

In early syphilis, the results of penicillin therapy are conditioned largely by two factors: (1) the duration of the disease; and (2) the time-dose relationships of penicillin administration.

As with all other forms of therapy, the earlier in the course of syphilitic infection penicillin treatment is begun, the better are the results. In the Army,[2] the failure rate in secondary syphilis was more than four times that of patients treated in the primary stage of the disease.

There is ample evidence, both from the clinic [3] and from the laboratory [4]

[1] MAHONEY, J. F., ARNOLD, R. C., and HARRIS, A.: Penicillin treatment of early syphilis: preliminary report, Ven. Dis. Inform., 1943, xxiv, 355.

[2] News and Comments: Status of penicillin treatment of early syphilis, Bull. U. S. Army Med. Dept., 1946, v, 1.

[3] MCDERMOTT, W., BENOIT, M., and DUBOIS, R.: Time-dose relationships of penicillin therapy: regimens used in early syphilis, Am. Jr. Syph., Gonor. and Ven. Dis., 1945, xxix, 345.

[4] EAGLE, H., MAGNUSON, H. J., and FLEISCHMAN, R.: The effect of the method of administration on the therapeutic efficacy of sodium penicillin in experimental syphilis, Bull. Johns Hopkins Hosp., 1946, lxxix, 168.

that the therapeutic effectiveness of penicillin is profoundly influenced by the time-dose relationships of its administration. Penicillin, unlike arsenic, is not bound by spirochetal organisms and its activity appears to depend upon the length of time during which therapeutically effective levels are available at the site of action. Precisely what the minimum effective level is and how long it must be maintained have not yet been determined. It is clear, however, that penicillin is actively treponemicidal in extremely low concentrations. It is also evident that relatively low concentrations acting over long periods of time are far more efficacious than high concentrations of brief duration. Increasing the tissue levels of penicillin, by giving higher dosages per injection does tend to increase its therapeutic effectiveness in the treatment of syphilis, at least up to a certain point. Of far greater importance, however, appears to be the time period over which *T. pallidum* is exposed to the action of the drug. Increased total doses of penicillin thus influence the results of therapy more if used to prolong the course of treatment than if given to augment the blood level at any one time.

The necessity of hospitalization for patients receiving penicillin as therapy for syphilis significantly reduces its general utility, for the number of hospital beds available for this purpose is limited, despite the Rapid Treatment Center program of the United States Public Health Service.

To be feasible as an agent for treatment of ambulatory syphilis patients in the clinic and in the physician's office, a modified penicillin with prolonged activity is desirable. Many attempts have been made to extend the duration of penicillin action, either by delaying its absorption or by blocking its renal tubular excretion, but by far the most satisfactory modification presently available is the suspension of penicillin in peanut oil and beeswax ("POB").[5]

"POB" has been used in the treatment of syphilis. Preliminary reports[6, 7] suggest that the results may be sufficiently satisfactory to warrant more widespread application. Treatment schedules utilizing "POB," alone and in combination with mapharsen or bismuth are being evaluated currently by the clinics coöperating in the nationwide syphilis study. Already there is some indication that with as much as 9.6 million units of penicillin in oil and beeswax over a period of 16 days, there is a not inconsiderable number of treatment failures.

Indeed, with any schedule of penicillin administration the results of which are presently available, there has been a high incidence of treatment failures.[8] "Relapse" rates after the Army employed 2,400,000 units in seven and one-half days have been several times as high as those after any schedule

[5] ROMANSKY, M. J., and RITTMAN, G. E.: Method of prolonging action of penicillin, Science, 1944, c, 196.

[6] KOCH, R. A.: Ambulatory intensive treatment of syphilis with calcium penicillin in oil and wax, Urol. and Cut. Rev., 1946, l, 461.

[7] ROMANSKY, M. J., and REIN, C. R.: Treatment of early syphilis with calcium penicillin-oil-beeswax, Jr. Am. Med. Assoc., 1946, cxxxii, 847.

[8] Committee on Medical Research and the United States Public Health Service: The treatment of early syphilis with penicillin, Jr. Am. Med. Assoc., 1946, cxxxi, 265.

of arsenobismuth therapy, prolonged or intensive (provided that the latter were fully completed).

There is here involved the possibility that penicillin actually may be more efficacious in early syphilis than appears from this comparison, and that many so-called relapses actually represent reinfection.[9] Unfortunately, this point is incapable of determination on the basis of existing clinical and experimental data.

It is believed that this excessively high incidence of treatment failures from penicillin may be reduced in two ways. The total duration of therapy may be prolonged, in which case there arises the problem of case-holding, so frequently encountered during metal chemotherapy. Perhaps a more promising approach is the addition to the penicillin treatment scheme of concurrently administered metal chemotherapy.

Eagle and his co-workers [10] have demonstrated that when penicillin and oxophenarsine hydrochloride are administered concurrently to syphilitic rabbits, the therapeutic effects not only are additive but actually synergistic. This important laboratory observation has been studied by the clinics cooperating in the penicillin study, and the clinical results following the use of penicillin with an arsenoxide have proved superior to those with penicillin alone. Administered in combination with bismuth, the immediate clinical results also have been superior to those with penicillin alone.

It must be recognized, however, that the concurrent administration of arsenicals introduces a risk of serious reactions in direct proportion to the total amount of the drug given, and in inverse proportion to the time interval over which it is administered.

In view of this and other considerations, there is no unanimity of opinion as to the desirability of combining penicillin and oxophenarsine hydrochloride in the routine treatment of early syphilis. Some have expressed the belief that the results with penicillin alone, when administered in adequate amounts over a long enough period of time, are satisfactory in a sufficiently large proportion of patients to justify eliminating arsenicals from the original course of treatment, reserving their use for relapsing cases. Others believe that the additional therapeutic effectiveness provided by arsenic warrants the increased risk.

In the management of neurosyphilis, penicillin is proving of significant worth. Upon the cerebrospinal fluid abnormalities and especially upon the pleocytosis and elevated protein content, which have been considered an indication of the "activity" of the process in the central nervous system (Dattner-Thomas [11]), penicillin exerts a profoundly favorable effect. This is true

[9] Editorial: The changing concept of reinfection with syphilis and its applicability as a criterion of cure, Am. Jr. Syph., Gonor. and Ven. Dis., 1945, xxix, 474.

[10] Eagle, H., Magnuson, H. J., and Fleischman, R.: The synergistic action of penicillin and mapharsen (oxophenarsine hydrochloride) in the treatment of experimental syphilis, Jr. Ven. Dis. Inform., 1946, xxvii, 3.

[11] Dattner, B., Thomas, E. W., and Wexler, G.: The management of neurosyphilis, 1944, Grune and Stratton, New York.

not only in asymptomatic neurosyphilis,[12] but also in the various clinical syndromes of syphilis of the central nervous system,[13] although post-treatment "reactivation" has been noted somewhat more frequently among those with symptomatic (usually parenchymatous) neurosyphilis than among those with asymptomatic involvement of the neuraxis.

In asymptomatic neurosyphilis, where the only evidence of involvement of the central nervous system is an abnormal spinal fluid, the results of therapy can be adjudged only by the response of the spinal fluid and the incidence of progression to clinical neurosyphilis. The spinal fluid abnormalities in early and late asymptomatic neurosyphilis respond dramatically to penicillin. Improvement is manifest promptly on cell count and protein content, more gradually on the colloidal test, and last of all, on the Wassermann reaction. Spinal fluid normality, once achieved, seems usually to be stable. The rapidity with which the spinal fluid becomes normal following penicillin therapy is dependent upon the degree of the pre-treatment abnormalities and the duration of the syphilitic infection. Lesser degrees of abnormality and those occurring within the first two years of the disease disappear rapidly; those more extensive and of longer duration improve slowly over a period of years.

The ultimate result in terms of clinical progression will not be known for many years. If, however, the favorable spinal fluid responses thus far noted are sustained, the incidence of clinical neurosyphilis developing in this group of patients should be low.

The clinical manifestations of neurosyphilis are protean: some due to active inflammation, others to degenerative processes; some reversible, others the result of irreparable damage of neural tissues. In its effects upon these clinical manifestations, which include such widely dissimilar symptom complexes as acute syphilitic meningitis, general paresis, tabes dorsalis, and Erb's spastic paraplegia, the presently available information suggests that penicillin is superior to metal chemotherapy but that it gives little promise of clinical results in parenchymatous neurosyphilis superior to those obtainable with fever therapy.

It should be pointed out, however, that such improvement as does follow penicillin therapy is attained at no risk to the patient, and in a shorter time and with less inconvenience to him than attends either therapeutic fever or protracted metal chemotherapy.

In acute syphilitic meningitis, the results of therapy with penicillin used alone are excellent,[14] but in parenchymatous neurosyphilis, less outstandingly favorable. In at least one clinic which has used both penicillin alone and penicillin as an adjunct to malarial fever therapy, greater success in general

[12] Moore, J. E., and Mohr, C. F.: Penicillin in the treatment of neurosyphilis. I. Asymptomatic neurosyphilis, Am. Jr. Syph., Gonor. and Ven. Dis., 1946, xxx, 405.

[13] Reynolds, F. W., Mohr, C. F., and Moore, J. E.: Penicillin in the treatment of neurosyphilis. III. Changes in cerebrospinal fluid abnormalities, Ann. Int. Med. (In press.)

[14] Nelson, R. A., and Moore, J. E.: Acute syphilitic meningitis treated with penicillin: a progress report, Am. Jr. Syph., Gonor. and Ven. Dis., 1946, xxx, 227.

paresis [15] and in tabes dorsalis [16] has been obtained with the combined therapy. There also are indications that penicillin alone may prove inferior to malaria plus penicillin in primary optic atrophy, late syphilitic nerve deafness, and Erb's spastic paraplegia.

For the present at least, there is reason to believe that the concurrent administration of penicillin with malarial fever therapy offers the patient with late parenchymatous neurosyphilis the greatest promise of a favorable outcome. It is probably the treatment of choice, therefore, in those forms of neurosyphilis which carry a serious risk to life or important bodily function: namely, paresis and taboparesis, primary optic atrophy and nerve deafness. In acute syphilitic meningitis, early or late asymptomatic neurosyphilis and in meningovascular neurosyphilis, therapy with penicillin alone may be given initially with good prospects of a favorable response.

The therapeutic problems in tabes dorsalis and in Erb's spastic paraplegia require further consideration. In each, the outlook ultimately is for distressingly chronic invalidism. Since, however, the evolution of these conditions is gradual, with no immediate threat to life or vital bodily function, and since these patients frequently are in such poor general physical condition as to be poor fever therapy risks, it is not unreasonable first to employ a form of therapy (e.g. penicillin) which is completely safe, provided there is any reasonable prospect that such therapy may be beneficial. In tabes dorsalis there is such a prospect, but in Erb's spastic paraplegia [17] there appears to be none.

Prior to the advent of penicillin, it was believed desirable to follow malaria therapy with a prolonged course of metal chemotherapy, not only to consolidate the effects of the fever but also to prevent progression of the disease in other organs, particularly in the cardiovascular system. The concomitant use of penicillin may well obviate the necessity for subsequent chemotherapy and thus significantly reduce the total duration of treatment.

Moreover, with penicillin, the advantages of fever therapy have been extended to that group of patients who are unsuitable for the rigorous full course of inoculation malaria. Rose and his co-workers [18] believe their results with an abbreviated course of malaria, given concomitantly with penicillin, were as satisfactory as those with a full course of malaria alone.

Gummatous lesions of the skin and bony skeleton,[19] and of such viscera as the liver [20] heal under therapy with penicillin. The healing process is no

[15] Reynolds, F. W., Mohr, C. F., and Moore, J. E.: Penicillin in the treatment of neurosyphilis. II. Dementia paralytica, Jr. Am. Med. Assoc., 1946, cxxxi, 1255.

[16] Chesney, L. P., and Reynolds, F. W.: Penicillin in the treatment of neurosyphilis. IV. Tabes dorsalis. To be published.

[17] Tucker, H. A.: Penicillin treatment of Erb's syphilitic spinal spastic paraplegia, Bull. Johns Hopkins Hosp., 1946, lxxviii, 161.

[18] Rose, A. S., Trevett, L. D., Hindle, J. A., Prout, C., and Solomon, H. C.: Penicillin treatment of neurosyphilis, Am. Jr. Syph., Gonor. and Ven. Dis., 1945, xxix, 487.

[19] Dexter, D. D., and Tucker, H. A.: Penicillin treatment of benign late gummatous syphilis: a report of twenty-one cases, Am. Jr. Syph., Gonor. and Ven. Dis., 1946, xxx, 211.

[20] Tucker, H. A., and Dexter, D. D.: Treatment of gummatous hepatic syphilis with penicillin: Report of two cases, Arch. Int. Med., 1946, lxxviii, 313.

more rapid than with metal chemotherapy. Inflammatory ocular lesions respond quickly, excepting interstitial keratitis where the results are no better than with older forms of therapy.

In cardiovascular syphilis and in late latent syphilis, the evaluation of the usefulness of any therapeutic agent involves many years of post-treatment observation. There is, as yet, therefore, no information as to the results of penicillin therapy in these conditions. Caution has been urged in the use of large initial doses of penicillin in the presence of overt cardiovascular syphilis, in view of the possible complications from therapeutic shock.

It is obvious, however, that treatment with penicillin offers nothing to those with late latent syphilis whose serologic tests remain positive following prolonged chemotherapy. To subject these patients to further therapy of any kind, solely for the purpose of attaining seronegativity, is to kindle false hopes and to waste time, money and effort.

In the prevention of prenatal infection through treatment of pregnant women with syphilis, penicillin has been highly efficacious. Here it probably is, as Goodwin and Moore [21] suggest, the present therapy of choice. Penicillin readily passes the placental barrier and its treponemicidal action is available to the fetus in utero. It appears, despite the contentions of some, not to provoke uterine contractions and not to precipitate premature labor. The outlook for a nonsyphilitic child following penicillin therapy is excellent. Even among those mothers whose syphilitic infection has been recently acquired and in whom the risk to the child is great, there have been remarkably few treatment failures.

Those treating patients with syphilis have in penicillin a drug of negligible toxicity, readily administered, but with definite limitations in therapeutic effectiveness. It is far from being the ideal form of treatment. Yet it has, for the present at least, a place in the treatment of syphilis as the most desirable form of therapy presently available for certain of the protean manifestations of this disease, and as an adjunct to older methods in others.

F. W. R.

[21] Goodwin, M. S., and Moore, J. E.: Penicillin in prevention of prenatal syphilis, Jr. Am. Med. Assoc., 1946, cxxx, 688.

# REVIEWS

*Carbohydrate Metabolism.* By SAMUEL SOSKIN, M.D., Director of the Research Institute, Michael Reese Hospital; Medical Director, Michael Reese Hospital; and Professorial Lecturer in Physiology, University of Chicago; and RACHMIEL LEVINE, M.D., Director of Metabolic Research and Endocrine Research, Michael Reese Hospital. 315 pages; 25 × 17.5 cm. 1946. University of Chicago Press, Chicago, Ill. Price, $6.00.

This volume fills a need for a comprehensive review of carbohydrate metabolism. It was written to serve as a text for students in biochemistry, physiology, and medicine but it should prove valuable to anyone interested in any phase of metabolism. The authors have presented their subject from a broad point of view and have therefore included various aspects of protein and fat metabolism, pointing out the artificial barriers which have separated the teaching of these subjects in the past.

The volume is divided into five main sections: the biochemistry and energetics, introductory physiological considerations, critical survey of the classical criteria of diabetes, the rôle of the endocrine glands in carbohydrate metabolism, and integration of physiological and clinical aspects. Numerous tables, illustrations and diagrams are helpful in following the complex relationships of various factors which influence the metabolic processes. The selected bibliography contains over 1200 references to original sources of significant experimental facts, to useful reviews, and to discussions of topics which could not be included in this volume.

The authors have drawn freely on the results of their own research in carbohydrate metabolism and have stressed the overproduction theory of diabetes. Whether or not one agrees entirely with their conclusions on the mechanism of the high blood sugar in diabetes mellitus, one is impressed with the extensive studies on carbohydrate utilization in the intact and the eviscerated animal which they have carried out during the past few years. One feels, however, that some of the fundamental studies on enzymes and enzyme systems could have been presented in a little greater detail. It is regrettable that the epoch-making discovery of Cori and his associates that insulin counteracts the inhibition of hexosekinase by one of the anterior pituitary hormones is not fully discussed.

This volume should prove extremely useful to anyone interested in metabolism as it coördinates a great deal of material which is not otherwise readily available.

M. A. A.

*Currents in Biochemical Research.* Edited by DAVID E. GREEN. 486 pages; 24 × 16.5 cm. 1946. Interscience Publishers, Inc., New York. Price, $5.00.

"Currents in Biochemical Research" consists of 31 essays on various biochemical topics written by authorities in their respective fields. Their aim has been to strip their presentations of highly technical terminology without sacrificing accuracy so that workers in related fields may follow the progress made and recognize the unsolved problems in biochemistry outside their own specialty. The essays are not intended to be extensive reviews but rather to point out the highlights in recent work. The papers are on a wide variety of subjects, biochemical problems related to pharmacology, chemotherapy, public health and genetics on the one hand and organic and physical chemistry applied to biochemical research on the other. One is impressed that in seemingly widely divergent topics, enzymes and enzyme systems are coming to be a common meeting ground for biochemists.

A number of chapters should be of interest to those in medical fields. These include short discussions by Dr. C. H. Best on insulin and diabetes, histamine and histaminase, heparin, lipotropic factors, and war medical research. The mucolytic enzymes, lysozyme and hyaluronidase are discussed in one paper and their possible

relationship to streptococcus infections and rheumatic fever is pointed out. Dr. C. L. Hoagland has written on "Biochemical Problems Posed by Diseases of the Muscle." With the constant broadening of scientific horizons one appreciates a volume of this type which presents authoritative information on many topics.

M. A. A.

## BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Endocrine Function of the Hypophysis.* By HARRY B. FRIEDGOOD, M.D. 828 pages; 24 × 16 cm. 1946. Oxford University Press, New York. Price, $4.50.

*The Chest.* A Handbook of Roentgen Diagnosis. By LEO G. RIGLER, M.D. 352 pages; 21 × 14.5 cm. 1946. Year Book Publishers, Chicago. Price, $6.50.

*Ulcer of the Stomach, Duodenum and Jejunum.* By RALPH C. BROWN, M.D. 172 pages; 24 × 16 cm. 1946. Oxford University Press, New York. Price, $2.25.

*Modern Development of Chemotherapy.* By E. HAVINGA, H. W. JULIUS, H. VELDSTRA and K. C. WINKLER. 175 pages; 21 × 15 cm. 1946. Elsevier Publishing Company, Inc., New York-Amsterdam. Price, $4.00.

*Medical Research.* A Symposium. Edited by AUSTIN SMITH, M.D. 169 pages; 24 × 16 cm. 1946. J. B. Lippincott Company, Philadelphia. Price, $5.00.

*Intracranial Complications of Ear, Nose and Throat Infections.* By HANS BRUNNER, M.D., University of Illinois. 444 pages; 23.5 × 15.5 cm. 1946. Year Book Publishers, Inc., Chicago. Price, $6.75.

*The Differential Diagnosis of Jaundice.* By LEON SCHIFF, Ph.D., M.D. 313 pages; 21 × 14.5 cm. 1946. Year Book Publishers, Chicago. Price, $5.50.

*Introduction to Surgery.* By VIRGINIA KNEELAND FRANTZ, M.D., and HAROLD DORTIC HARVEY, M.D. 216 pages; 19 × 12.5 cm. 1946. Oxford University Press, New York. Price, $2.50.

*Eye Manifestations of Internal Diseases.* Second Edition. By I. S. TASSMAN, M.D., University of Pennsylvania. 613 pages; 25 × 17 cm. 1946. The C. V. Mosby Company, St. Louis. Price, $10.00.

*Some Chapters in Cambridge Medical History.* Sir WALTER LANGDON-BROWN, Emeritus Professor of Physic in the University of Cambridge. 119 pages; 19.5 × 13 cm. 1946. Cambridge; at the University Press, New York, The Macmillan Company. Price, $1.75.

*La Preparacion de Soluciones "Tipo"—Para el Analisis Volumetrico.* By WALTER JUNG and CARLOS E. CARDINI. 90 pages; 24 × 17 cm. 1946. Biblioteca Central de la Universidad Nacional de Tucuman, Tucuman-R. Argentina.

*Menstrual Disorders and Sterility.* Second Edition. By CHARLES MAZER and S. LEON ISRAEL. 570 pages; 24 × 16.5 cm. 1946. Paul B. Hoeber, Inc., New York. Price, $7.50.

*Cor Pulmonale.* By J. CODINA-ALTES, M.D. 205 pages; 23.5 × 17 cm. 1944. Libreria Editorial, Cientifico Medica Espanola, Madrid.

# COLLEGE NEWS NOTES

## Life Members

The College is gratified to announce that the following Fellows, listed in order of their subscription, have become life members of the College:

Dr. Andrew C. Blair, F.A.C.P., Charlotte, N. C., November 18, 1946
Dr. Paul F. Liva, F.A.C.P., Lyndhurst, N. J., November 21, 1946
Dr. J. K. Williams Wood, F.A.C.P., Troy, Pa., November 25, 1946
Dr. C. DeWitt Briscoe, F.A.C.P., Panama, R. P., December 5, 1946
Dr. Carrol C. Turner, F.A.C.P., Memphis, Tenn., December 5, 1946
Dr. J. Russell Twiss, F.A.C.P., New York, N. Y., December 13, 1946
Dr. William R. Blue, F.A.C.P., Memphis, Tenn., December 16, 1946
Dr. William M. Sheppe, F.A.C.P., Wheeling, W. Va., December 16, 1946
Dr. Hildegarde G. Sinnock, F.A.C.P., Quincy, Ill., December 16, 1946

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## A.C.P. Dues Restored to Former Rate

Prior to 1933, College dues were $20.00 per annum for Fellows and $15.00 for Associates ($10.00 in case of full-time teachers, military officers, research workers, et al.). On January 1 of that year, due to the depression, the dues were reduced to $15.00 and $12.00 respectively (the minimum $10.00 dues continuing to apply in case of full-time teachers, etc.).

On October 20, 1946, the Board of Regents voted unanimously to restore the dues to the former rates. Everything costs materially more now; College services and activities have been tremendously increased; the journal costs at least 35 per cent more to publish; the College cannot continue its broad program or plan desired expansions without increased dues.

The Action by the Board of Regents was taken after careful study and analysis. The College dues are considerably less than those of most other national medical societies. Even in some state medical societies, the dues are as high as $50.00 per annum (in one state society, $100.00).

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The Annual Regional Dinner Meeting of the College, Southern California Chapter, will be held on February 7 at the Alexandria Hotel, Los Angeles, under the direction of Dr. Leland Hawkins, A.C.P., Governor for the district.

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## Hotel Reservations—Chicago Annual Session

The American College of Physicians has been guaranteed adequate hotel accommodations for all the physicians who desire to attend its Annual Session at Chicago, April 28 to May 2, inclusive, 1947, but the Chicago Convention Bureau and the Chicago hotels have requested the College to clear all reservations through a Housing Committee.

Hotels with which official arrangements have been made, and all of which are in fairly close proximity to the headquarters hotel, the Palmer House, include the Stevens, Morrison, Congress, Sherman, Chicagoan and Bismarck. All reservations at these hotels must be cleared through the Housing Committee. Those desiring to stay at other hotels in Chicago may arrange their reservations personally and directly.

All hotel applications received up to January 1, 1947, were handled by the Executive Office of the College; all applications thereafter are referred to the Housing Committee. The form suggested for application is as follows:

HOUSING COMMITTEE
AMERICAN COLLEGE OF PHYSICIANS
The Chicago Convention Bureau
33 N. LaSalle St.
Chicago 2, Ill.

Hotel Reservations for the period of the American College of Physicians Annual Session, Chicago, April 28–May 2, are requested as follows:

Hotel preferred: ————————; 2nd choice: ————————
Type of room: ( ) Single; ( ) Double; ( ) Double, twin beds;
( ) Suite, twin bedded room and parlor.
Price range per day: $———— to $————
Date of arrival: ————————; date of departure ————————
Name and address:

*Single Rooms:* Very few single rooms are available. Attendants are urged to share twin bedded rooms with acquaintances or friends. The Housing Committee has only 350 single rooms at its disposal.

*The Palmer House,* as official headquarters, will house all Officers, Regents and Governors of the College, Speakers on the program and Distinguished Guests. These reservations will be handled personally by the Executive Secretary of the College, and applications from this group should be submitted only to the Executive Secretary.

*Technical Exhibitors:* The Technical Exhibitors will be housed at the Congress Hotel as their official headquarters. Exhibitors may apply directly to Mr. Daniel Amico, Sales Manager of the Congress Hotel, identifying themselves with the meeting of the American College of Physicians.

Applications for hotel accommodations to the Housing Committee will be promptly acknowledged; the Committee will clear all applications once weekly with the Convention Bureau: each hotel will be requested to confirm reservations assigned to it.

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## INDEX AND SUMMARY OF REGISTRATIONS, AUTUMN COURSES, 1946

| No. | Title | Institution | Director | Dates |
|---|---|---|---|---|
| 1. | Internal Medicine | University of Pittsburgh School of Medicine, Pittsburgh, Pa. | Dr. R. R. Snowden | September 2–14 |
| 2. | Psychosomatic Medicine | University of Colorado School of Medicine and Hospitals, Denver, Colo. | Dr. Franklin G. Ebaugh | September 23–28 |
| 3. | Internal Medicine | University of Oregon Medical School, Portland, Ore. | Dr. Homer P. Rush | October 7–19 |
| 4. | Clinical Neurology | Jefferson Medical College, Philadelphia, Pa. | Dr. Bernard J. Alpers | October 14–18 |
| 5. | Clinical Medicine from the Hematologic Viewpoint | Ohio State University College of Medicine, Columbus, Ohio | Dr. Charles A. Doan | October 21–26 |
| 6. | Internal Medicine | Gallinger Municipal Hospital, Washington, D. C. | Dr. Wallace M. Yater | Oct. 21–Nov. 1 |
| 7. | Allergy | Roosevelt Hospital, New York, N. Y. | Dr. Robert A. Cooke | November 4–9 |
| 8. | Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease | Massachusetts General Hospital, Boston, Mass. | Dr. Paul D. White | November 4–9 |
| 9. | Gastro-enterology | University of Chicago School of Medicine, Chicago, Ill. | Dr. Walter L. Palmer | November 11–16 |

| No. | Title | Institution | Director | Dates |
|---|---|---|---|---|
| 10. | Selected Problems in Internal Medicine | Western Reserve University and Affiliated Hospitals, Cleveland, Ohio | Dr. Joseph M. Hayman, Jr. | November 18–23 |
| 11. | Internal Medicine | McGill University and Royal Victoria Hospital, Montreal, Que. | Dr. J. C. Meakins | Nov. 25–Dec. 6 |
| 12. | Bacterial Chemotherapy | Washington University School of Medicine, St. Louis, Mo. | Dr. W. Barry Wood, Jr. | December 2–7 |
| 13. | Cardiology | University of Michigan Medical School, Ann Arbor, Mich. | Dr. Frank N. Wilson | December 2–7 |

| No. | Fellows | Associates | Non-members | TOTAL |
|---|---|---|---|---|
| 1. | 6 | 5 | 15 | 26 |
| 2. | 13 | 4 | 2 | 19 |
| 3. | 4 | 6 | 4 | 14 |
| 4. | 25 | 11 | 12 | 48 |
| 5. | 36 | 19 | 20 | 75 |
| 6. | 20 | 12 | 24 | 56 |
| 7. | 11 | 5 | 9 | 25 |
| 8. | 56 | 19 | 0 | 75 |
| 9. | 20 | 21 | 26 | 67 |
| 10. | 5 | 13 | 12 | 30 |
| 11. | 20 | 7 | 8 | 35 |
| 12. | 10 | 3 | 1 | 14 |
| 13. | 31 | 9 | 0 | 40 |
| | 257 | 134 | 133 | 524 |

During the Spring, 1946, the College conducted ten courses, with a registration of 334 Fellows, 151 Associates and 199 Non-Members; Total, 684.

Summary of Registrations for the Year, 1946:

591 Fellows
285 Associates

876 A.C.P. Members
332 Non-Members

1,208 Grand Total

## POSTGRADUATE COURSES, SPRING 1947

The detailed Postgraduate Bulletin, Spring, 1947, is now available, and copies have been mailed to all members of the College and to non-members who have had their names placed on the Mailing List.

Fees for all courses, except No. 1, are $20.00 per week for A.C.P. Members; $40.00, for Non-Members. Fee for Course No. 1, $40.00 for Members; $80.00 for Non-Members.

All registrations must be made on the official registration form obtainable from the Executive Office of the College, 4200 Pine St., Philadelphia 4, Pa.

### SCHEDULE

| No. | Title | Institution | Director | Dates |
|---|---|---|---|---|
| 1. | Growth, Isotopes and Tumor Formation | Lankenau Hospital Research Institute, Philadelphia, Pa. | Dr. S. R. Reimann | February 3–8 |
| 2. | Cardiovascular Disease | University of Southern California School of Medicine, Los Angeles, Calif. | Dr. G. C. Griffith | February 3–8 |
| 3. | Peripheral Vascular Disease | Mayo Foundation, Univ. of Minn. Rochester, Minn. | Dr. E. V. Allen | March 17–22 |

| No. | Title | Institution | Director | Dates |
|---|---|---|---|---|
| 4. | Arthritis & Allied Conditions | Mayo Foundation, Univ. of Minn. Rochester, Minn. | Dr. P. S. Hench | March 24–29 |
| 5. | Cardiovascular Disease | Emory University School of Medicine, Atlanta, Ga. | Dr. R. Bruce Logue | March 31–April 5 |
| 6. | Internal Medicine | University of Michigan Medical School, Ann Arbor, Mich. | Dr. C. C. Sturgis | April 7–12 |
| 8. | Cardiovascular Disease | Northwestern University Medical School, Chicago, Ill. | Dr. J. Roscoe Miller | April 21–26 * |
| 7. | Cardiovascular Disease | Philadelphia General Hospital, Philadelphia, Pa. | Dr. Francis C. Wood & Dr. Calvin Kay | May 12–17 |
| 9. | Internal Medicine | University of Cincinnati College of Medicine, Cincinnati, Ohio | Dr. M. A. Blankenhorn | May 26–June 7 |

* Course No. 7 immediately precedes the A.C.P. Annual Session in Chicago, April 28– May 2.

## The Committee on Postwar Medical Service Now Known as Joint Committee for the Coördination of Medical Activities

Early in World War II, The American College of Physicians, The American Medical Association, and The American College of Surgeons established a joint Committee on Postwar Medical Service. Representation on the Committee was soon extended to many other national medical and hospital organizations, and meetings have been held monthly through the intervening years. On October 12, 1946, the name of the Committee was changed to "The Joint Committee for the Coördination of Medical Activities," with the concurrence and approval of each participating organization.

During the War years, the Committee was concerned almost wholly with postwar planning. In recent months the Committee has been concerned with industrial health, physical fitness, and other matters on which discussions in a group of this sort should help to crystallize medical opinion. It is a joint committee concerned with medical planning, not active in itself until its associate organizations have concurred in planned proposals. Represented on the present Committee are the Offices of the Surgeons General of the U. S. Army, U. S. Navy, and U. S. Public Health Service, the Federation of State Medical Boards, the American and Catholic Hospital Associations, the Advisory Board for Medical Specialties, and several others.

The meeting of this Committee on October 12, 1946, covered discussions on the following subjects:

> The Bureau of Information of the American Medical Association, re handling location problems of physician veterans; Surplus Property; Intern and Residency Opportunities; The Resident Program for Physician Veterans; Licensure; a Specialty Board for General Practitioners; Establishment of Medical Corps in Veterans' Administration; Rural Medical Service; Industrial Health; Physical Fitness; Automobile Priorities for Physicians; Data on Army Separations, etc.

## Reports on Recent Regional Meetings

### *Chicago, November 16, 1946*

The Annual Regional Meeting of The American College of Physicians for the territory embracing Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota, and Wisconsin was held at the Congress Hotel, Chicago, November 16, 1946, with an attendance of 425 physicians. College Governors for the participating states acted as presiding officers and coöperated in the preparation of the program, selecting

speakers from each territory. The program, although limited to one full day of presentations, was considered an outstanding one, and this was borne out by the full attendance of physicians at every part of the program, continuing to the concluding paper. At the Luncheon Meeting Dr. LeRoy H. Sloan, F.A.C.P., Regent and General Chairman of the 1947 Annual Session of the College, spoke at length on the preparations for the meeting, details concerning the program, and other relevant matters. At the Dinner Meeting in the evening, at which numerous distinguished guests were present, Dr. David P. Barr, F.A.C.P., President of the College, made an address on the historical development and purposes of the College, and Dr. Andrew C. Ivy, F.A.C.P., Vice President and Distinguished Professor of Physiology, University of Illinois College of Medicine, and Assistant Dean of Northwestern University, gave an address on "War Crimes of a Medical Nature," his address dealing with the medical war crimes in Germany during the recent war.

*Memphis, Tenn., November 22, 1946*

A Regional Meeting of the College for the territory embracing Arkansas, Louisiana, Mississippi, Tennessee, and Texas was held at Memphis, November 22, 1946, under the Governorship of Dr. William C. Chaney of Memphis, with the cooperation of the College Governors for the other states. Dr. William D. Stroud, Philadelphia, gave an address on Coronary Artery Disease; Dr. Conley Sanford, F.A.C.P., Dr. William C. Colbert, F.A.C.P., and Dr. Douglas Sprunt, F.A.C.P., of the University of Tennessee College of Medicine, Memphis, conducted a Clinical Pathologic Conference; Dr. H. Packer of the Division of Preventive Medicine, University of Tennessee College of Medicine, gave an address on "New Knowledge in the Treatment of Malaria"; Dr. Walter L. Palmer, F.A.C.P., of the University of Chicago, The School of Medicine, made a presentation on "Treatment of Intractable Peptic Ulcer"; and Dr. Hugh Morgan, F.A.C.P., President-Elect of the College, and Professor of Medicine at Vanderbilt University, Nashville, gave a paper on "Hypertension." In the evening a dinner was given at the Memphis Country Club in honor of Dr. Hugh Morgan as President-Elect of the College. Mr. E. R. Loveland, Executive Secretary of the College, Philadelphia, presented a report on the activities of the College during the current year. Dr. William D. Stroud, F.A.C.P., Philadelphia, introduced Dr. Morgan who made a most interesting philosophical address on the professions, with special regard to medicine and the relationship of The American College of Physicians.

The scientific program was restricted to a small number of speakers but each speaker was given an adequate time to cover thoroughly his subject. The program was exceedingly well received and the attendance was approximately 300.

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Dr. Thomas Parran, F.A.C.P., Surgeon General of the U. S. Public Health Service, has announced that the Service will receive to May 1, 1947, applications from physicians for training in an accredited school of public health during academic year 1947–48. The purpose of the Fellowships is to provide trained health officers to fill the many vacancies which exist in state and local health departments. Full details may be secured from The Surgeon General, U. S. Public Health Service, 19th and Constitution Aves., N. W., Washington 25, D. C. (Attention Public Health Training.)

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In its seventh Annual Essay Contest, the Mississippi Valley Medical Society will offer a cash prize of $100, a gold medal, and a certificate of award for the best unpublished essays on a subject of general medical interest and value to the general practitioner of medicine. Contestants must be members of the American Medical

Association and residents of the United States. The winner will be invited to present his contribution before the next annual meeting of the Society, which will be held at Burlington, Iowa, October 1–3, 1947. The Society reserves the right to publish the essays in its publication. Contributions should not exceed 5,000 words and should be submitted in quintuplicate not later than May 1, 1947, to Dr. Harold Swanberg, F.A.C.P., Secretary of the Society, 209–224, W.C.U. Bldg., Quincy, Ill.

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A meeting of the Antibiotics Study Section of the National Institute of Health will be held in Washington, D. C., January 31 and February 1, 1947. Representatives of Government agencies, commercial producers, and investigators concerned with antibiotics are invited to attend this conference. Expenses, unfortunately, cannot be defrayed by the Bureau of Public Health Service. Inquiries concerning the meeting and the presentation of scientific reports should be addressed to Dr. Gordon Seger, Executive Assistant, National Institute of Health, Bethesda 14, Md.

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Drs. Francis J. Braceland, F.A.C.P., Rochester, Minn., Arthur Carlisle Christie, F.A.C.P., Washington, D. C., and William S. Middleton, F.A.C.P., Madison, Wis., have been appointed members of a special advisory group concerned with assisting General Omar N. Bradley, Administrator of Veterans Affairs, and Dr. Paul R. Hawley, F.A.C.P., chief of the Veterans Administration's Department of Medicine and Surgery, in developing over-all policies for medical services.

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Dr. Julius Chasnoff, F.A.C.P., New York, N. Y., received the Army Commendation Ribbon for his services with the Thomas M. England General Hospital. The citation read in part, "service with the Medical Department has been exceptional when compared with others of the same grade of similar position, and I wish to commend you for your outstanding contribution as Chief of Medical Service, Executive Officer and President of the Army Retiring Board at the Thomas M. England General Hospital, Atlantic City, N. J., from October 1945, to May 1946."

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Speakers at the Fourth Annual Medical and Surgical Symposium, Watts Hospital, Durham, N. C., February 12, 1947, will include Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio; Dr. Monroe J. Romansky (Associate), Washington, D. C.; Dr. Howard F. Root, F.A.C.P., Boston; Dr. Albert M. Snell, F.A.C.P., Rochester, Minn.; and Dr. Francis C. Wood, F.A.C.P., Philadelphia.

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Brig. Gen. Robert M. Hardaway, U. S. Army, F.A.C.P., has been awarded the Legion of Merit. As commanding officer of the Bushnell General Hospital, August, 1942, to January, 1946, Dr. Hardaway is said to have "developed a superior program for amputee patients throughout the Ninth Service Command."

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Brigadier General Eugen C. Reinartz, formerly commandant of the AAF School of Aviation Medicine, Randolph Field, Texas, has retired from active duty with the Army after twenty-nine and a half years of service. He entered the Service in 1919, being assigned to the Aeronautics Division of the Aviation Section, Signal Corps, and had continuous service with aeronautics thereafter. He went to both the English and North African Theaters of War as aeromedical observer to study problems confronting flight surgeons in combat. He received the John Jeffries Award for exceptional contributions to the advancement of aeronautics through medical research, in 1943, the award being given by the Institute of Aeronautical Sciences. It is said he has had the longest continuous service of any medical officer in the Army Air Forces.

Col. Charles T. Young, U. S. Army (Associate), has received the Oak Leaf Cluster to the Legion of Merit. The citation related that as commanding officer of the Wakeman Convalescent Hospital, Dr. Young "displayed a high type of organizational ability and leadership."

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Dr. Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army, has been awarded the Cross of the Legion of Honor from the French Government.

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Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, has been awarded the Officer's Cross of the Royal Order of Leopold the Second by the Prince Regent of Belgium. The award recognizes Dr. Geiger's "distinguished services rendered to Belgium and for unusual resourcefulness as an administrator of public health."

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Dr. Marcus A. Feinstein (Associate), of New York, N. Y., has been awarded the Army Commendation Ribbon. The commendation recognizes the valuable addition to medical knowledge from Dr. Feinstein's study of an outbreak of acute respiratory disease which occurred in bomber squadrons returned from overseas. Dr. Feinstein retired from the Army of the United States with rank of Major, April, 1946.

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Dr. Leon Unger, F.A.C.P., Chicago, was elected President of the American College of Allergists at its meeting in San Francisco last June.

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Dr. Virgil P. Sydenstricker, F.A.C.P., Augusta, Ga., has been awarded the King's Medal by King George VI. The award recognizes Dr. Sydenstricker's distinguished service to the British Government during World War II.

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Dr. William P. Corr, F.A.C.P., Riverside, Calif., who retired with rank of Colonel from the Medical Corps, Army of the United States, in January, 1946, has been awarded the Legion of Merit. The citation speaks of Dr. Corr's "meritorious service at Dibble General Hospital, Menlo Park, Calif., from October 1943 to June 1945," his "wide knowledge of all phases of internal medicine, quiet yet forceful leadership and high ideals . . . administrative ability."

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### Admiral McIntire Retires from Post of Surgeon General

It was recently announced that Vice Admiral Ross T. McIntire, F.A.C.P., had retired from the position of Surgeon General of the U. S. Navy, and would shortly retire from the Service. Dr. Clifford A. Swanson has been appointed by the President to succeed Dr. McIntire, with rank of Rear Admiral.

Dr. McIntire received his M.D. degree from Willamette University in 1912. He entered the Medical Corps of the Navy in 1917, and became Surgeon General in 1939. Dr. McIntire's administrative ability and professional zeal are said to have contributed largely to the effectiveness of the Bureau of Medicine & Surgery in preparing for and dealing effectively with the medical problems of the past war.

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### Dr. Robert B. Radl, F.A.C.P., Bismarck, N. D., Appointed A.C.P. Governor for North Dakota

Owing to the recent death of Dr. Julius O. Arnson, College Governor for the State of North Dakota, and in accordance with provisions of the Constitution and By-Laws, Dr. David P. Barr, President, has appointed Dr. Robert B. Radl, F.A.C.P., Bismarck, as interim Governor to complete the unexpired term of the late Dr. Arnson.

### Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to December 13, 1946 inclusive).

William B. Adamson, Abilene, Tex. (Lt. Col., MC, AUS)
George R. Callender, Washington, D. C. (Brig. Gen., MC, USA)
Everett LeCompte Cook, Martinsburg, W. Va. (Col., MC, USA)
W. Lee Hart, Dallas, Tex. (Brig. Gen., MC, USA)
Ellis H. Hudson, Athens, Ohio (Capt., MC, USNR)
Noble D. Leonard, Downey, Ill. (Capt., MC, USNR)
George L. Leslie, Howell, Mich. (Lt. Col., MC, AUS)
Adolph B. Loveman, Louisville, Ky. (Major, MC, AUS)
Eugen G. Reinartz, San Francisco, Calif. (Brig. Gen., MC, USA)
Paul B. Roen, Los Angeles, Calif. (Comdr., MC, USNR)
William H. Roper, Denver, Colo. (Major, MC, AUS)
Joseph M. Ryan, Oak Ridge, Tenn. (Lt. Col., MC, AUS)
Paul L. Shallenberger, Chicago, Ill. (Col., MC, AUS)
Norman S. Skinner, Saint John, N. B., Can. (Major, RCAMC)
Arthur G. Sullivan, Hot Springs National Park, Ark. (Comdr., MC, USNR)
Julius Wolfram, Dallas, Tex. (Capt., MC, AUS)

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### *Correction*

It was erroneously stated in the August issue (page 391) that Dr. Julius Chasnoff, F.A.C.P., retired from the Army Medical Corps prior to July 12, 1946, with rank of Lieutenant Colonel. Dr. Chasnoff's separation from the service was completed November 2, 1946; at that time he held the rank of Colonel.

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## MINUTES OF THE BOARD OF REGENTS

### Philadelphia, Pa., October 20, 1946

The regular autumn meeting of the Board of Regents was held at the College Headquarters, Philadelphia, October 20, 1946, with President David P. Barr presiding and Mr. E. R. Loveland acting as Secretary, and with the following in attendance:

David P. Barr ..... *President*
Hugh J. Morgan ..... *President-Elect*
James J. Waring ..... *First Vice President*
A. B. Brower ..... *Second Vice President*
William D. Stroud ..... *Treasurer*
George Morris Piersol ..... *Secretary-General*
Charles T. Stone .....
Walter B. Martin .....
William S. Middleton .....
James E. Paullin .....
LeRoy H. Sloan .....
George F. Strong .....
William S. McCann .....
T. Grier Miller .....
Charles F. Moffatt .....
Maurice C. Pincoffs ..... *Editor,* Annals of Internal Medicine
Chauncey W. Dowden ..... *Chairman, Board of Governors*
Edward L. Bortz ..... *Chairman, Advisory Committee on Postgraduate Courses*

The Secretary read abstracted Minutes of the preceding meetings of the Board of Regents, which were approved as read.

The Secretary then read communications from various members of the Board of Regents who could not be present, and from the following:

(1) Dr. Ward Darley, F.A.C.P., Denver, Colo.—asking the College to consider ways and means of making it possible for members of the College to deduct from Federal Income Tax Returns expenses incurred as a result of attending Postgraduate Courses conducted by the College.

It was the opinion of the Board that this matter ought to be handled individually in different districts, and should be taken up directly with the local Collector of Internal Revenue.

(2) Dr. David P. Barr, F.A.C.P., New York, N. Y., President—reporting that Dr. G. Gill Richards, F.A.C.P., Salt Lake City, Utah, had been the official representative of the American College of Physicians at the inauguration of the new President of the University of Utah.

(3) Dr. David P. Barr, F.A.C.P., New York, N. Y., President—reporting that Dr. Nelson G. Russell, Sr., Buffalo, N. Y., had been the official representative of the American College of Physicians at the Centennial Celebration of the University of Buffalo, October 3–4, 1946.

(4) Dr. David P. Barr, F.A.C.P., New York, N. Y. President—reporting that Dr. Joseph M. Hayman, Jr., F.A.C.P., Cleveland, Ohio, has been appointed as official representative of the College at the proposed meeting of the International Congress of Tropical Medicine and Malaria, to be held in the United States at an early date.

(5) Dr. Herman H. Riecker, F.A.C.P., Ann Arbor, Mich.—giving details of the last illness of the late Dr. James D. Bruce and concerning a floral tribute supplied at his funeral on behalf of the College.

(6) Dr. George D. Mallory, Assistant Secretary, University of California—acknowledging receipt of and expressing the gratitude of the Regents of the University for a check for $3,840.00, representing tuition fees collected by the College for a Postgraduate Course at that institution during June, 1946.

(7) Dr. Alexander H. Colwell, F.A.C.P., Pittsburgh, Pa.—requesting permission for one or more medical residents to attend the annual meeting of the American College of Physicians.

Dr. Colwell had already been informed that the College would be pleased to grant them the courtesy of admission.

(8) The Executive Office of the College—notifying members of the Board of the privilege to obtain Air Travel Cards for official College travel.

(9) A Regent of the College—quoted partially as follows: "What are we doing as a College to insure that our members are keeping up with progress in medicine?' How many of them are getting about and trying to absorb a bit more of the cheapest commodity on the present market? Why should not the College sponsor a concentrated course for members of the Board of Regents and Board of Governors, which would include only the very newest in medical research and progress? Then why not sponsor a series of publications, to be distributed to members only, in the form of question and answer, which would cover in the period of three months the whole field of the newer chemistry, biology, physiology, pathology, etc., related to Internal Medicine. . . .

President Barr stated that the new College Marshal, Dr. T. Grier Miller, Philadelphia, would appreciate suggestions from the Board about the conduct of the Convocation, and stated that he had in mind some changes that would be helpful.

*Report* of the SECRETARY-GENERAL—Dr. George Morris Piersol: "The following 35 Fellows and 6 Associates have died since the last meeting of this board:

*Fellows*

| | | |
|---|---|---|
| Anderson, William Wesley | Fort Thomas, Ky. | April 2, 1946 |
| Barnhart, Grant Samuel | Washington, D. C. | July 25, 1946 |
| Baxmeier, Robert Ivan | Pittsburgh, Pa. | June 27, 1946 |
| Bertolet, William S. | Reading, Pa. | October 9, 1946 |
| Bisaillon, Marr | Portland, Ore. | June 3, 1946 |
| Bissell, Wayne W. | Rockford, Ill. | September 6, 1946 |
| Bruce, James D. | Ann Arbor, Mich. | September 5, 1946 |
| Carr, Earl Curtis | M.C., U. S. Navy | May 9, 1946 |
| Chase, Harrison A. | Falmouth, Mass. | July 23, 1946 |
| Cohen, Mortimer | Pittsburgh, Pa. | June 20, 1946 |
| Craven, Erle Bulla, Jr. | Lexington, N. C. | June 19, 1946 |
| Dozzi, Daniel Louis | Philadelphia, Pa. | May 18, 1946 |
| Foster, Benjamin B. | Portland, Maine | May 8, 1946 |
| Frick, Anders | Chicago, Ill. | May 9, 1946 |
| Gordon, Murray B. | Brooklyn, N. Y. | June 29, 1946 |
| Holmes, Champneys Holt | Atlanta, Ga. | June 12, 1946 |
| Huber, Edward | M.C., U. S. Army | July 23, 1946 |
| Jensen, Walter Steen | M.C., U. S. Army | April 4, 1946 |
| Levy, I. Harris | Syracuse, N. Y. | July 9, 1946 |
| Libman, Emanuel | New York, N. Y. | June 28, 1946 |
| MacNeal, Ward J. | New York, N. Y. | August 15, 1946 |
| McGovern, Louis Vincent | Brooklyn, N. Y. | April 29, 1946 |
| Moyer, Torrence C. | Lincoln, Nebr. | September 8, 1946 |
| Palmer, Donald Ainslie | Spokane, Wash. | June 10, 1946 |
| Scott, W. Mastin | Shreveport, La. | July 21, 1946 |
| Smith, Eben Elliott | M.C., U. S. Navy | June 16, 1946 |
| Soiland, Albert | Los Angeles, Calif. | May 14, 1946 |
| Solway, Leon Judah | Toronto, Ont., Canada | December 14, 1945 |
| Spangelberger, Mathew Arnold | Denver, Colo. | June 9, 1946 |
| Spector, Hyman I. | St. Louis, Mo. | July 6, 1946 |
| Stevens, Rollin H. | Detroit, Mich. | May 17, 1946 |
| Thomas, John D. | Washington, D. C. | July 15, 1946 |
| Twyman, George Thomas | Independence, Mo. | October 4, 1946 |
| Wilcox, Clark Anson | Wichita Falls, Tex. | April 4, 1946 |
| Wilson, Robert, Sr. | Charleston, S. C. | May 20, 1946 |

*Associates*

| | | |
|---|---|---|
| Barnes, James R. E. | Cicero, Ill. | June 16, 1946 |
| Barthelme, Francis Lorraine | Effingham, Ill. | March 8, 1946 |
| Curry, Grove P. M. | Mount Kisco, N. Y. | May 13, 1946 |
| Kirkland, Clyde W. | Bellaire, Ohio | March 25, 1946 |
| Morris, Alanson F. B. | Pittsburgh, Pa. | February 6, 1946 |
| Scott, Joseph Eckles | Portland, Ore. | April 23, 1946 |

On the occasion of Dr. Bruce's death, President Barr, Secretary Loveland and others, wrote personal letters to Mrs. Bruce, and an appropriate floral tribute was furnished through Dr. Herman H. Riecker on behalf of the Officers, Regents and Governors of the College. Do you not think we should have a resolution inserted in the Minutes which shall also go to Dr. Bruce's family?"

. . . On motion by Dr. Hugh J. Morgan, seconded by Dr. Charles T. Stone, and carried, a resolution was adopted approving the above, and President Barr requested

Dr. Hugh J. Morgan to prepare such a resolution for insertion in the Minutes and transmission to Mrs. Bruce. . . .

. . . A special notice was also taken on the death of Dr. Robert Wilson, Sr., Charleston, S. C., who was formerly a Governor of the College. . . .

"Since the last meeting of the Board, the following additional 5 Fellows have become Life Members of the College, bringing the grand total to 493, of whom 42 are deceased, leaving a balance of 451:

| | |
|---|---|
| Leo E. Westcott | Kalamazoo, Mich. |
| Morris Deitchman | Youngstown, Ohio |
| Arthur Ernest Moon | Temple, Tex. |
| George Foster Herben | Yonkers, N. Y. |
| Gustav Leonard Kaufmann | Chicago, Ill. |

. . . On motion by Dr. James E. Paullin, seconded by Dr. George F. Strong, and carried, the report of the Secretary-General was accepted. . . .

*Report* of the EXECUTIVE SECRETARY—Mr. E. R. Loveland: "Practically all items that would be included in the Executive Secretary's Report will be brought out through Committee deliberations and reports following. Our Regional Meeting program received such a stimulus during the War that it is continuing with the same enthusiasm and interest. It was our thought that after our Annual Sessions are resumed emphasis would be placed primarily on State Regional Meetings, which have a real value in a more intimate and personal way than the larger multi-State meetings. However, there is a tendency for the Governors to continue their multi-State plan in many instances. The following is the schedule of meetings already held or planned:

| Territory | City | Date | Chairman |
|---|---|---|---|
| Western Pennsylvania | Pittsburgh | Sept. 11, 1946 | R. R. Snowden |
| Virginia | Virginia Beach | Oct. 15, 1946 | J. W. Preston |
| Western New York | Syracuse | Oct. 16, 1946 | E. C. Reifenstein, Sr. |
| North Carolina | Winston-Salem | Oct. 18, 1946 | P. F. Whitaker<br>E. L. Persons |
| Western Michigan | Grand Rapids | Oct. 30, 1946 | B. R. Corbus |
| Florida, Alabama, Georgia, and South Carolina | Miami Beach | Nov. 3–4, 1946 | T. Z. Cason |
| New Jersey | Newark | Nov. 8, 1946 | G. H. Lathrope |
| Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota and Wisconsin | Chicago | Nov. 16, 1946 | W. L. Palmer |
| Tennessee | Memphis | Nov. 22, 1946 | W. C. Chaney |
| New England | Hanover, N. H. | Jan. 28, 1947 | H. T. French |
| Eastern Pennsylvania and Delaware | Philadelphia | Feb. 7, 1947 | E. L. Bortz |
| Oklahoma | Oklahoma City | Feb. 22, 1947 | Wann Langston |

There is a definitely growing interest in College membership, with an ever-increasing number of inquiries and proposals for membership. I predict there will be no less than 350 candidates for Associateship and 250 candidates for Fellowship. The last meeting of the Board of Regents being held late in the spring (May, 1946) and this autumn's meeting being held much earlier than usual created a much shorter period between meetings than customary. Even so we have prepared for the Credentials Committee 108 candidates for Fellowship and 183 candidates for Associateship. It must be remembered that the intervening period has been primarily a summer season, too.

There is a tremendous increase in College work. More than 30,000 inquiry cards have been mailed out this year concerning candidates. Especially has the ANNALS OF INTERNAL MEDICINE forged ahead in popularity, both as a scientific journal and as an advertising medium. The advertising volume has

increased 60% since July 1, 1939; the circulation has increased 85% since July 1, 1939, a considerable proportion of this being during the past year. Contrary to our anticipation that with the ending of the War, the Army and Navy would discontinue their orders and the circulation would fall off, the Army and Navy have continued a fair proportion of their orders, and the profession has greatly multiplied its number of subscriptions. 1946 income from subscriptions will be over $53,000.00, which means the handling of more than 9,000 individual subscription items. The advertising income will be nearly $22,000.00, which represents the handling of many different accounts. As a matter of fact, the business now entailed in handling the "Annals" alone greatly excels all the business combined in the College a few years back. Publishing Regional Meeting programs and forms and arranging the details likewise entail a real extension in the work of the College.

I am gratified to report that we have an improved office personnel over that of the past two or three years. There is an improvement in the type and in their ability, and Mr. Pindar, who is now with us on full time, is establishing a promising record."

. . . The Executive Secretary's report was opened for discussion. Dr. LeRoy H. Sloan, a member of the Committee on Credentials, pointed out that there is a tremendous amount of work and expense involved in handling the inquiry cards on candidates, and that a fairly large proportion are returned as "unknown." He suggested it is time to consider some other technic of obtaining information about candidates, such as the establishment of a Committee of the Governors, or some other means. Mr. Loveland stated that the card system works wholly satisfactorily in smaller States and smaller communities and has a definite value, but that in large communities, such as New York City, there is such a large number of members that, obviously, candidates are known to a comparatively small percentage thereof. However, the card system is provided for in our By-Laws and on our proposal form. . . .

. . . On motion by Dr. James E. Paullin, seconded by Dr. Hugh J. Morgan, and carried, it was

RESOLVED, that this question be referred to the Committee on Credentials, to report some recommendation at a later date.

*Report* of the COMMITTEE ON CREDENTIALS—Dr. George Morris Piersol, Chairman: "The Committee on Credentials reviewed the proposals of 108 candidates for Fellowship and 183 candidates for Associateship. An analysis of its recommendations is as follows:

| | | |
|---|---|---|
| (A) Candidates for FELLOWSHIP: | | |
| Recommended for Advancement to Fellowship | 59 | |
| Recommended for Election Directly to Fellowship | 14 | 73 |
| Recommended for Election First to Associateship | | 3 |
| Deferred | | 31 |
| Rejected | | 1 |
| Total | | 108 |
| (B) Candidates for ASSOCIATESHIP: | | |
| Recommended for Election | | 123 |
| *Fellowship Candidates Recommended for Election first to Associateship | | 3 |
| Deferred | | 43 |
| Rejected | | 17 |
| | | 183, plus *3 |

The Committee, therefore, recommends the election of the following 73 candidates to Fellowship. (List published in the November, 1946, issue of this journal.)

. . . On motion by Dr. George Morris Piersol, seconded by Dr. William D. Stroud, and carried, the above 73 candidates were formally elected to Fellowship. . . .

"The Committee recommends the election of the following 126 candidates to Associateship. (List published in the November, 1946, issue of this journal.)

. . . On motion by Dr. James E. Paullin, seconded by Dr. William D. Stroud, and carried, the above 126 candidates were officially elected to Associateship. . . .

"The Credentials Committee submits the following report on candidates elected to Associateship five years ago, December 14, 1941:

| | |
|---|---|
| Already Advanced to Fellowship | 57 |
| Deceased | 1 |
| Dropped for Failure to Qualify for Advancement to Fellowship | 12 |
| Time Extended because of Military Service | 30 |
| | 100 |

The following Associates from the Class of December 14, 1941, are entitled to a certain extension of time, due to military service:

| | |
|---|---|
| Allday, Louis Edgar | Dallas, Tex. |
| Burket, L(ouis) Clair | Altoona, Pa. |
| Caldwell, John W. G. | Des Moines, Iowa |
| Carson, Leon Delwin | M. C., U. S. Navy |
| Chapman, Kenneth William | U. S. Public Health Service |
| Davis, John Kemp | M. C., U. S. Army |
| Foster, William Bell | M. C., U. S. Army |
| Green, Eugene Willard | U. S. Public Health Service |
| Kilgore, Floyd Vern | M. C., U. S. Army |
| Kilgore, Newton Alvin, Jr. | Houston, Tex. |
| Lawson, Dwight | M. C., U. S. Army |
| Liston, David Ernest | M. C., U. S. Army |
| Lyman, Harold Dwight | U. S. Public Health Service |
| Main, Emory Hendon | Philippi, W. Va. |
| McCarty, David Wilson, Jr. | Longmont, Colo. |
| Morrison, Albert Taylor | U. S. Public Health Service |
| Nelson, Kenneth Roy | U. S. Public Health Service |
| Ossenfort, William Frederick | U. S. Public Health Service |
| Pinckney, Norton Morris | Richmond, Va. |
| Power, Frank Kenneth | Salem, Ore. |
| Price, Frank Lewis | U. S. Public Health Service |
| Rinck, Edward Clinton | U. S. Public Health Service |
| Royce, Owen, Jr. | Milwaukee, Wis. |
| Shallenberger, Paul Lawrence | Chicago, Ill. |
| Stone, Robert Edwards, | Birmingham, Ala. |
| Telfer, James Gavin | U. S. Public Health Service |
| Vaughn, John Orren | Santa Monica, Calif. |
| Vogel, Stoughton Ralph | Philadelphia, Pa. |
| Voorhies, Norton William | New Orleans, La. |
| Wallace, C(harles) Stewart | Ithaca, N. Y. |

Twelve Associates who were not on military service have not fulfilled the requirements and under conditions of the By-Laws must now be dropped.

The Credentials Committee has seriously taken up the question of the use of the

inquiry cards concerning candidates, and it would welcome suggestions or any plan from any member of the Board of Regents. The present system is very expensive, unwieldy and not too successful."

. . . By resolution the report of the Committee on Credentials was accepted as a whole. . . .

*Report* of the COMMITTEE ON SURVEY—Dr. William S. Middleton, Chairman: "The Regents will recall that there were a number of suggestions involved in the task of the Survey Committee, largely to reconcile and clarify the requirements for Fellowship and Associateship. It also undertook to insert into the Constitution and By-Laws a clause that would implement Mastership.

## ARTICLE V

### ELECTION OF FELLOWS

*Section 1.* A Fellow of the College shall have met the following qualifications and requirements:

(a) He shall have qualified and served a minimum period of three years as an Associate, except upon recommendation of the Committee on Credentials by reason of very special qualifications as hereinafter set forth.

(b) He shall have been graduated from a medical school acceptable to the Board of Regents, at least five years prior to the time of his election, and if engaged in practice, his professional activity must be confined to the field of internal medicine or a related specialty.

(c) If he is not a bona fide teacher or permanent laboratory worker, he shall have been in the actual practice of internal medicine or an allied specialty at a permanent location for at least three years preceding nomination for Fellowship. The Committee on Credentials, with the approval of the Board of Regents, shall be given discretionary power to modify this ruling under exceptional conditions.

(d) The criteria of eligibility for election to Fellowship are bi-lateral:

1. Detailed information concerning the candidate's hospital and academic appointments, with particular reference to the size and nature of the hospital service and the exact teaching responsibility; published contributions in media acceptable to the Committee on Credentials, with particular emphasis upon papers published during the period of Associateship; personal approval by Fellows in his territory, with reference to his character, ethical standing and medical activities; evidence of postgraduate training and attendance upon the Annual Meetings of the College.

2. He shall be certified by the recognized national board of certification in his particular field, where such an accrediting board exists. This regulation, however, shall not apply to candidates from civilian life who were elected to Associateship prior to April 6, 1940, nor to such candidates from the Army, Navy and Public Health Service who were elected prior to and including April 1, 1944.

### PROPOSAL

*Section 2.* His name shall be proposed in writing by a Master or Fellow of the College from the same state, province or territory, not an officer or member of the Board of Regents; he shall be seconded by another Master or Fellow from the same state, province or territory and endorsed by the member of the Board of Governors from the state, province or territory in which he resides, or by the Surgeon General of the Army, Navy or Public Health Service or the Medical Director of the Veterans Administration, or by an officer of the College or by a member of the Board of Regents. His nomination must be accompanied by an adequate written statement made both by the proposer and the seconder, containing all of the above cited qualifications of

the candidate. Furthermore, the name of the candidate shall be sent to each Fellow in the Candidate's locality with the request for comments as to the candidate's fitness. The proposer must be prepared to add such further information as may be requested by the Committee on Credentials.

*Section 3.* The credentials of the candidate shall be considered by the Committee on Credentials, which Committee shall report to the Board of Regents for election or rejection.

Successful candidates shall be so notified immediately after their election and shall be urged to attend the next succeeding Convocation, when Fellowships will be formally conferred. The official Fellowship Certificate, signed by the President and the Secretary-General, shall be issued following the Convocation. Acknowledgement of its receipt shall be made upon an official card, signed and dated by the newly elected Fellow, and returned to the Executive Secretary, to be added to the official College roll.

*Section 4.* Proposals for direct election to Fellowship, with or without prior certification by the appropriate certifying board, may be made to the Committee on Credentials. This manner of election is an unusual mark of distinction; hence such candidates must be preëminent in teaching, research or clinical practice. In advancing individuals for such consideration, the following details must be furthermore considered: maturity, national reputation, publications and other contributions to medical science and public welfare. The Committee on Credentials will exercise due discrimination in all proposals for direct election to Fellowship.

This ruling will not be invoked for candidates who have failed of regular advancement from Associateship to Fellowship.

## ARTICLE VI

### Election of Masters

*Section 1.* A special committee on Masterships will be named by the President. This committee will consist of two members from the Board of Regents and one member from the Board of Governors. It will bring its nominations of Master to the Board of Regents for election or rejection.

## ARTICLE VII

*Section 1.* An Associate of the College shall have met the following qualifications and requirements:

(a) He shall hold the degree of M.D., M.B., or M.D., C.M., from a medical school acceptable to the Board of Regents.

(b) After receiving his medical degree, the candidate shall have had at least one year internship in an approved hospital and three years of organized graduate training in internal medicine or allied fields, or its equivalents, approved by the Committee on Credentials and the American Board of Internal Medicine. One year of this graduate training may be spent in the basic sciences.

(c) He shall be a member in good standing in his local, state, provincial or territorial and national medical societies, except in the case of those not engaged in practice, such as full-time teachers, research workers, and those holding official hospital and similar positions.

(d) If a practitioner, he shall be licensed to practice medicine in his state, province or territory, and shall indicate his purpose to confine his practice to internal medicine or an allied specialty from the date of his application, or be a Medical Officer in the Government Service, either in the United States or the Dominion of Canada, in American or Foreign Service. If not a practitioner, he shall hold an official in-

stitutional position in internal medicine, an allied branch of internal medicine or in medical research.

### Proposal

*Section 2.* His name shall be proposed on the official blank of the College by a Master or Fellow residing in the same state, province or territory, not an officer or member of the Board of Regents; he shall be seconded by another Master or Fellow also from the same state, province or territory, and endorsed by the member of the Board of Governors from the state, province or territory in which he resides, or by the Surgeon General of the Army, Navy or Public Health Service or the Medical Director of the Veterans Administration; or in special instances, by an Officer of the College or by a member of the Board of Regents.

*Section 3.* The credentials of candidates for Associateship shall be considered first by the Committee on Credentials, which Committee shall report to the Board of Regents for election or rejection.

Successful candidates shall receive at once, from the Board of Regents through the Executive Secretary, an appropriate official notification of their election to Associateship in the College.

### Term of Associateship and Eligibility for Fellowship

*Section 4.* Candidates so elected shall be continued as Associates for a term not to exceed five years.

The Associate will be eligible for election to Fellowship at the end of three years. Upon expiration of this three year period he shall be notified in writing by the Committee on Credentials of his eligibility for election to the Fellowship during the next two years, provided he has met the requirements necessary for Fellowship within that time. If he is not elected to Fellowship within five years, his Associateship is automatically terminated. The Committee on Credentials, with the approval of the Board of Regents, shall be given discretionary power to modify this ruling under exceptional conditions."

. . . The report was opened for general discussion. In regard to certification, it was pointed out that Canadian candidates, under the new provisions, by referring to "National" instead of "American" may qualify through certification by the Royal College of Physicians of Canada, and that candidates from the Caribbean and Central American countries would have to satisfy the standards of the United States. Dr. Strong referred to a number of Canadian physicians who have qualified as Fellows of the Royal College of Physicians of London, whose examinations are reported to be much more difficult than those in the United States, and inquired whether there is any provision to cover these men. Dr. Middleton said there was none, that the Survey Committee felt the machinery within the Dominion of Canada would take care of such cases, especially if reciprocal recognition exists. Dr. Strong replied that such reciprocal recognition would be established in Canada.

Dr. LeRoy H. Sloan inquired, if criteria for election to Fellowship are bi-lateral, is a physician who is not certified by his Board ever eligible? Dr. Middleton replied that he may be eligible for direct election, and referred to that section dealing with proposals for direct Fellowship. Dr. Sloan further inquired about a physician who becomes an Associate of the College and thereafter turns to full-time teaching or research, for which there is no certifying board. Dr. Middleton replied that he could still qualify for Fellowship under the new regulations, without certification.

President Barr inquired about the case of the internist in small towns. Dr. Middleton stated that the Committee realized fully that many of these men would

be excluded, because they will be doing some obstetrics, minor surgery, etc., and that the Committee thought unquestionably the College would wish to discriminate between the man who is practicing general medicine and the one who is truly an internist. Dr. Piersol pointed out that the Credentials Committee is confronted frequently with the problem of the candidate who is essentially an internist, but who does general practice, some obstetrics and some limited surgery. The Committee considers that they do not fall within the proper category of the definition of an internist, and he expressed the belief that this provision is a wise one. Dr. Middleton further pointed out that this regulation was put in because the Committee on Credentials feels that this is the time at which the candidate should be apprised of the ideals of the American College of Physicians. It should define clearly at the outset of a candidate's entrance as an Associate whether or not he is going to be a general practitioner or an internist.

Dr. James J. Waring inquired about the significance of the term "allied specialty." Dr. Middleton pointed out that the College numbers among its members many specialists other than internists, such as Pediatricians, Neuropsychiatrists, Laboratorians, Dermatologists and Radiologists, and that this term refers to them.

Dr. Piersol suggested that inasmuch as this proposal by the Committee on Survey will be published to the members that the same clause which now exists in the By-Laws, namely, that election of a Fellow shall be in accordance with the By-Laws as stated and such additional rules of the Board of Regents that they from time to time may adopt, shall be inserted. This provision has proved most valuable and it provides for modification of the rules by action of the Board of Regents without the formal process of amending the By-Laws. Dr. Middleton stated this suggestion was acceptable.

. . . On motion by Dr. Hugh J. Morgan, seconded by Dr. William D. Stroud, and regularly carried, the report of the Committee on Survey was accepted, and it was planned that the proposal be circulated to all members of the Board of Regents and Board of Governors before the next joint meeting of those Boards.

Dr. Hugh J. Morgan spoke at length on behalf of the general practitioner, whose allegiance by and large is to the College in terms of interest and aspirations, but whose practice at the moment precludes him from College membership. He requested the Board of Regents to consider in the broad planning whether there is a role which the College can play in relation to the general practitioner. He said that in the group of general practitioners there is a small, but very important segment that aspires to quality, that looks to this College for help, stimulation and instruction. Dr. Morgan suggested the consideration of whether or not there might not be in the College not only the present group who can qualify for Fellowship, but a group of general practitioners of higher attainments who might be admitted to some Associate classification, and through that association the College might perform a fine function toward encouraging quality performance among a very important group of general practitioners.

Dr. Maurice C. Pincoffs supported Dr. Morgan's thought, but pointed out that it would be extremely difficult to set up differentials between the man who was described by Dr. Morgan and the present group who qualifies for regular membership. Furthermore, that it would include such a large number that the Annual Sessions of the College might be impossible to accommodate, physically and educationally.

*Report* of the COMMITTEE ON PUBLIC RELATIONS—Dr. James E. Paullin, Acting Chairman, in the absence of Dr. Roger I. Lee, Chairman: "The Committee has four communications:

(1) Dr. Ross G. Harrison, National Research Council, informing the College of and asking its participation in the United Nations Educational, Scientific and Cultural Organization, which has to do with the further establishment of peace.

The Committee feels this communication should be received as information and referred to the Executive Committee of the College for proper answer.

(2) Dr. W. C. Nalty, F.A.C.P., desiring the College to take some action whereby Fellowship in the College shall be recognized as equivalent to certification, entitling College members in the Veterans Administration to receive 25% increase in pay.

The Committee on Public Relations feels that this is not within the province of the College, and we recommend that Dr. Nalty be informed to that effect.

(3) Dr. Malcolm T. MacEachern, F.A.C.P., American College of Surgeons, Chicago, Ill., calling attention to the existence of unrest in the world today about the division between physicians, surgeons and general practitioners.

This communication was received as information.

(4) Dr. G. V. Brindley, seeking approval of the College of the resident training program of a Texas hospital.

Inasmuch as the College has established no department for this purpose, the Committee recommends this communication be referred to the Council on Medical Education and Hospitals of the American Medical Association."

. . . On motion by Dr. James E. Paullin, seconded by Dr. Hugh J. Morgan, and carried, this portion of the Committee's report was accepted and approved. . . .

"The Committee recommends the acceptance of the following resignations:

1. Dr. Stephen L. Lirot (Associate), Meriden, Conn.
2. Dr. Floyd C. Taggart (Associate), Topeka, Kan.
3. Dr. M. J. Tornatore (Associate), Clearfield, Pa."

. . . On motion by Dr. James E. Paullin, seconded by Dr. William D. Stroud, and carried, this recommendation was approved and the resignations accepted. . . .

"The Committee on Public Relations reviewed the following cases affecting fees and dues:

(1) *Dr. Charles A. Breck, F.A.C.P., Wallingford, Conn.*

Due to total disability and inability to engage in practice, the Committee recommends that his dues be waived, and that he be given the privilege of deferment in the payment of his original Initiation Fee until his return to work."

. . . On motion by Dr. James E. Paullin, seconded by Dr. Maurice C. Pincoffs, and carried, this action was approved. . . .

"(2) *Col. Elias Earle Cooley, F.A.C.P., (MC), USA, Retired.*

The Committee recommends that because of physical disability, his dues be waived until resumption of remunerative work."

. . . On motion by Dr. James E. Paullin, seconded by Dr. James J. Waring, and carried, this motion was approved. . . .

"(3) *Capt. W. A. Vogelsang, F.A.C.P., (MC), USN, Retired.*

The Committee recommends that his dues be waived so long as he is not in active practice, or until he resumes remunerative work."

. . . On motion by Dr. James E. Paullin, seconded by Dr. Hugh J. Morgan, and carried, this recommendation was approved. . . .

"The Committee had before it the disciplinary case of Dr. ———— (Associate), Ala., who became an Associate of the College by virtue of former membership in the American Congress on Internal Medicine. He has been convicted

of avoidance of payment of income tax, sentenced to the Federal Penitentiary and fined a large sum of money. We hold a copy of his indictment from the U. S. Court and the judgment and his commitment. The Committee recommends that he be summarily dropped from the College roll."

. . . On motion by Dr. James E. Paullin, seconded by Dr. Hugh J. Morgan, and carried, this recommendation was unanimously approved. . . .

"The Committee had some deferred business. On November 18, 1945, the Board of Regents referred to the Committee a consideration of whether to extend College membership beyond North America and its possessions. The present policy is to restrict membership to North American Countries and their dependencies, and, further, to physicians who read and speak English. The College has no machinery, under its present By-Laws, whereby candidates from other countries can qualify through our proposal system. On May 14, 1946, by resolution, without prejudice, this item of business was continued on the agenda of the next meeting of the Committee on Public Relations. The Committee at its meeting yesterday recommended that the membership of the College be restricted to its present boundaries, and that this matter be continued for future consideration by the Board of Regents."

. . . On motion by Dr. James E. Paullin, seconded by Dr. Charles T. Stone, and carried, the last recommendation on deferred business was approved, and the report as a whole was accepted. . . .

*Report* of the COMMITTEE ON CONSTITUTION AND BY-LAWS—Dr. James E. Paullin, Chairman: "There was referred to the Committee, consisting of Doctors Moffatt, Strong and Paullin, an amendment to the By-Laws, Article IV, Section 2, concerning the tenure of office of members of the Board of Governors. The Board of Regents on May 17, 1946, adopted a resolution providing that a proper by-law be prepared, providing for the limitation in the term of office of members of the Board of Governors to three consecutive terms of three years each, and that this by-law be presented for adoption at the next Annual Business Meeting of the College. To that end, the Committee recommends that the following added paragraph be made to Article IV, Section 2: 'The members of the Board of Governors shall each serve for a term of three years, and not more than three consecutive terms.'"

. . . On motion by Dr. James E. Paullin, seconded by Dr. William D. Stroud, and carried, the recommendation was approved. . . .

*Report* of the COMMITTEE ON FELLOWSHIPS AND AWARDS—Dr. James J. Waring, Acting Chairman, in the absence of Dr. Reginald Fitz, Chairman: "A lengthy report has been submitted by the Chairman, Dr. Fitz, which has received the careful consideration of the Committee. Research Fellowships in the past have been from one to three Research Fellows. Your Committee recommends this year that beginning July 1, 1947, an appropriation of $20,000.00 be made to guarantee not more than eight Research Fellowships, each to last for twelve months, at a stipend of $2,200.00 to $3,000.00. The old range of stipend was $1,800.00 to $2,500.00. The Committee at the insistence of Dr. Fitz recommends certain changes in phraseology in the paragraph of the Directory, referring to Research Fellowships, the revised copy to be as follows:

> 'In line with one of the objects of the American College of Physicians to promote and advance clinical research, on October 20, 1946, by resolution, the Regents of the College established eight Research Fellowships of the American College of Physicians in the amount of $2,200.00 to $3,000.00 to be awarded each year until further notice on the recommendation of the Committee on Fellowships and Awards and the approval of the Board of Regents. These fellowships are designed especially for the benefit of young physicians who are in the early stages of preparation for a teaching and investigative career in medicine.
> 'The Committee on Fellowships and Awards obtains its list of candidates by communicating with the Professors of Medicine and Pediatrics in the approved

medical schools of the country and with the Officers and members of the Board of Regents of the College. The Committee may also utilize, to such extent as it deems wise, the machinery of the National Research Council.'

"The Committee offers this modification in the belief that the description of the Research Fellowships as it has been printed in the Directory of the College is no longer complete, that the stipend originally offered is now too meager, and that the appointment of more than one Research Fellow of the College each year is at present desirable. The Committee recognizes that if this recommendation is adopted, the annual expenditure of approximately $20,000.00 of our income for this purpose must be authorized.

"*The James D. Bruce Fund*—it will be recalled that $10,000.00 was donated by the late Dr. Bruce, half to be allocated for a memorial to Dr. Alfred Stengel and half to an Annual Lectureship in Preventive Medicine. On May 12, 1946, the Board of Regents directed the Committee to confer with the President and Secretary-General for the purpose of setting up the James D. Bruce Fund and establishing policies and principles regarding its use.

"The Committee on Fellowships and Awards believes an Annual Lectureship in Preventive Medicine, named for Dr. Bruce, would be in accord with his wishes, would be a suitable memorial to him as a Fellow always deeply interested in the welfare of the College, and that such a lectureship would add to the interests of our Annual Sessions. The John Phillips Memorial Award was set up in 1929; it was first a money award and later changed to a medal. The Committee on Fellowships and Awards has authority, after due consultation with certain authorities, to make the selection and to make that award. The College in that instance reserves only the right of making no award if a sufficiently meritorious piece of work has not been recommended. We also refer to the Convocational Lectureship, and point out that by tradition the President has the sole responsibility for selecting the Convocational Lecturer. The Committee on Fellowships and Awards believes the James D. Bruce Lectureship and Award could be administered more wisely through a slightly different procedure than either of the above, and recommends the following policies and principles:

"The Fund shall be held by the Treasurer; that part of the income allocated to the Lectureship shall be awarded as a stipend to the lecturer, who shall be appointed annually for each year that the College holds a Session.

"The Board of Regents shall cause to be designed and prepared for the College a medal known as the James D. Bruce Memorial Medal. This shall be presented each year to the lecturer.

"The candidate to receive the award and medal in any year shall be nominated at least four months before the Annual Session of that year by the Committee on Fellowships and Awards. In making the nomination, the Committee may obtain the advice of the Officers, Regents and Governors of the College, and of Fellows appointed by the Committee as referees because of their expert knowledge in the field of Preventive Medicine. The Committee shall obtain the advice of the President; the candidate selected shall be eminent in any of the many divisions of Preventive Medicine.

"The nomination of the candidate shall be approved by the Board of Regents, making it mandatory that the Committee's choice first receive official approval by the President and later by the Board of Regents, or by the Executive Committee of the College.

"The candidate shall deliver a lecture at the Annual Session at which he receives the award. The lecturer shall be described in the program of the meeting as the 'James D. Bruce Memorial Lecturer in Preventive Medicine,' and shall deal with some phase of Preventive Medicine.

"The James D. Bruce Memorial Medal shall be appropriately awarded by the President to the lecturer of the year as a part of the Convocation ceremony. Each lecture shall be published in the ANNALS OF INTERNAL MEDICINE as promptly as possible after its delivery.

"This Fund also had a provision relating to the Alfred Stengel Memorial Award. The Committee has made no final decision on this particular point. The Committee recommends that the cost of preparing the James D. Bruce Memorial Medal be defrayed by the College and not by appropriation from the Fund given by Dr. Bruce.

"The Committee has not made a final selection of a recipient of the John Phillips Memorial Award.

"*Research Fellowship awarded to Dr. Tom Fite Paine, Jr.*—Finally, the Committee recommends that Dr. Tom Fite Paine, Jr., of Boston, he awarded a Research Fellowship, to begin July 1, 1947, in the amount of $3,000.00."

In the discussion that ensued, Dr. William D. Stroud raised the question as to whether it might not be better to offer, say, three Research Fellowships for a three-year period; that some think there are already too many one-year fellowships, that a man usually just gets started in a year's time, and if he is worth a fellowship, he ought to be allowed at least three years to carry out his proposed investigations. Dr. Waring replied that this had been considered by the Committee. Heretofore in the College it has not been the policy to make extensions of fellowships, that perhaps in view of the fact that there were a great many men coming back from military service, it would be advisable at this time to have more fellowships, rather than an extension of already designated fellowships. The Committee, however, recognizes that a man who undertakes to do research work cannot get very far in just one year, and that perhaps a two-year or three-year fellowship might be desirable—the question being whether this now is the appropriate time for such a change in policy. Furthermore, Dr. Waring expressed the opinion that the present policy does not preclude continuation of a fellowship if the Committee feels that the work in progress is in need of further continuation for completion.

. . . On motion by Dr. William D. Stroud, seconded by Dr. Maurice C. Pincoffs, and carried, the recommendations of the Committee on Fellowships and Awards were approved, and an appropriation of $20,000.00 was authorized and the report of the Committee accepted. . . .

President Barr pointed out that the Committee on Fellowships and Awards is unprepared to recommend any of the remaining seven possible Research Fellows, and suggested that it would seem expedient this year to give to the Committee authority to choose these fellows and to use its discretion in the amounts which are to be paid each fellow without the necessity of reference to this Board.

. . . On motion by Dr. William D. Stroud, seconded by Dr. LeRoy H. Sloan, and carried, this suggestion was approved. . . .

Dr. Waring, for the information of the Board, offered the following data concerning Dr. Tom Fite Paine, Jr., to whom a fellowship was awarded: age, 28; born, Aberdeen, Miss.; now a Research Fellow, Thorndike Memorial Laboratory, Boston City Hospital; Research Fellow, Department of Medicine, Harvard Medical School; married, has two children; references and teachers—Drs. Hugh J. Morgan and Maxwell Finland; had service in the Army; did hospital work with or under Drs. George R. Minot, William S. McCann and George M. Dack; wishes to work in infectious diseases, with regard to the use of antibiotics under Dr. Maxwell Finland; both Dr. Morgan and Dr. McCann endorsed his excellent record.

The Secretary, Mr. Loveland, asked for directions from the Board concerning the preparation of the James D. Bruce Memorial Medal, its inscription, etc.

. . . On motion by Dr. James E. Paullin, seconded by Dr. William D. Stroud, and carried, the President was directed to appoint a Committee to design a suitable

Medal, and to report back to the Board of Regents at its next meeting, with designs or models for final approval. . . .

(Thereafter, President Barr appointed Doctors George Morris Piersol and O. H. Perry Pepper a Committee of two.)

*Report* of the COMMITTEE ON THE ANNALS OF INTERNAL MEDICINE—Dr. T. Grier Miller, Acting Chairman, in the absence of Dr. Reginald Fitz, Chairman: "The following report was prepared in large part by Dr. Fitz before the meeting of the Committee.

"In May, 1942, Dr. Paul W. Clough was appointed to serve as Acting Editor of the ANNALS, to fill the place of Dr. Maurice C. Pincoffs, who had entered military service. He accepted this appointment in troubled times; he faced the possibility of a reduced circulation, dearth of material and financial loss; and then he encountered a shortage of paper, increased costs of printing and irksome delays in the submission of articles for publication and in the delivery by the printer of issues of the journal when finally in press. It was an outstanding achievement to conduct an important medical journal under such conditions, to maintain its literary and scientific integrity, to increase its popularity and to keep it on an even financial keel. The Committee reaffirms its gratitude to Dr. Clough and thanks him again for his loyalty, intrepidity and wisdom.

"When Dr. Clough became Acting Editor, the Board of Regents appointed Dr. W. Halsey Barker, of Baltimore, as Assistant Editor. Dr. Pincoffs has now reopened his desk, and thus the first recommendation of the Committee is threefold: that the Board of Regents welcome the return of Dr. Pincoffs to the ANNALS, with satisfaction as well as pride; that Dr. Clough be reappointed Assistant Editor, and that Dr. Barker receive the official thanks of the College for his services by vote of the Board of Regents and in the form of an appropriate personal letter signed by the President.

"The most baffling problem faced by the ANNALS at the moment is that of obtaining paper. The Executive Secretary commented on this at the May meeting of the Board of Regents, pointing out the neat decision to be made in determining the quantity of the journal to be printed when, on the one hand, new subscriptions were increasing in unexpected numbers and when, on the other, paper was becoming harder to procure. In June a partial compromise was effected whereby permission was granted to continue the use of the thinner 45 lb. stock paper that had been employed during the War, instead of the more attractive and luxurious 60 lb. paper. Now we are informed by our printers, the Lancaster Press, that the paper situation has not eased and indeed that no means of replenishment of dwindling stocks is immediately in view.

"Though reduced during the War by about 200 pages from its 2700 pages for the year of 1940, a pruning that was artfully accomplished, the Committee believes that still further pruning can be performed without lasting damage to the character and usefulness of the periodical. It now recommends, as emergency and temporary measures, the following:

(*a*) that the personal items in the News Notes Section be omitted, thus saving 6%;
(*b*) that the Obituary Notices not exceed 300 words, thus accounting for another 1%; and
(*c*) that the space devoted to scientific papers be reduced sufficiently to make a total reduction of 10%.

"The Committee approves the salary increases for the Assistant Editor and Secretary, and for the increase in budget to cover honoraria to editorial writers and for other special purposes as submitted to the Committee on Finance by the Editor. It also recommends, in keeping with the current increase in salaries, wages and cost of living, an increase of $600.00 in the salary of the Editor.

"The Committee asks for acceptance of this report and the adoption of the recommendations contained in it."

. . . On motion by Dr. Hugh J. Morgan, seconded by Dr. William D. Stroud, and carried, the above report was approved. . . .

*Report* of the EDITOR—Dr. Maurice C. Pincoffs: "The Editor has resumed his duties only for the last four weeks, and certainly feels that the ANNALS has made a great deal of progress in spite of the War. The Regents should thank the Acting Editor for a magnificent piece of work done by a man very heavily burdened with other tasks during the War, and he richly deserves an increase in salary, because of the work he has still to do as the Assistant Editor. At a later meeting I hope to bring before the Regents some thoughts about the future of the ANNALS. It is obvious that we are extending its influence well beyond our membership, and the journal is becoming one of the most widely circulated medical journals in its field, perhaps in the world. It seems to me, although its present policy of make-up obviously has won it that recognition, that responsibility might or should entail some additional contents, some other aspects, since it now returns such a large income. Possibly as an educational feature of the College, it should be expanded."

. . . The Editor's report was received and recorded. . . .

*Report* from the BOARD OF GOVERNORS—Dr. C. W. Dowden, Chairman: "This meeting of the Board of Regents, midway between the Annual Sessions, means that there is no meeting of the Board of Governors, and, consequently, no deliberations upon which to report. Each Governor was given the opportunity to submit any matter for discussion before this Board, but no problems were submitted. The Board of Governors seems to me to play a very small part in the conduct of the affairs of the College. That is not due to the College; it is not due to the Board of Regents; it is not due to anything except the Governors themselves have failed to set up the proper machinery for obtaining information that might be of great value to the Board of Regents. I think they were very helpful to the Committee on Survey, but aside from that and apart from their endorsing candidates and having representation on the Credentials Committee, they do very little. I am convinced that the Board of Governors could do a tremendous amount of work, and I have been thinking of two or three things: (1) the conduct of State meetings, rather than multi-State Regional Meetings. I don't believe the Board of Governors will ever function as it should when four or five States are put together for Regional Meetings. Those functions are enjoyable, the men enjoy the social side and there are some good speakers, but, after all, I do not think the Multi-State meetings contribute a great deal to the advancement of the College in a personal way in the several States. If the States will each continue to have their own meetings, I believe the plan will attract a far larger percentage of the Governors. For instance, through the War and up to date, Kentucky has been meeting with five or six other States in Chicago; Illinois probably has 80% or 90% attendance of its members, but from Kentucky we may have only 5% or 6%, and, therefore, the meeting doesn't do much good in Kentucky. I would favor an individual Kentucky meeting. In such a case, I could go back from a meeting like this, report on the matters discussed here, we would have a business session, and I could bring back to this Board not only what I think as Governor for Kentucky, but I could tell you what members as a whole of that State are thinking about; that would be a report worth while. I would like to be advised whether such a procedure seems feasible, because it seems to me we are not getting what the membership as a whole would like to have.

"Second, it is becoming more and more evident that the Committee on Nominations must select with great care proper Governors. If the State meetings are resumed, that Committee might well get an expression by secret ballot from the membership of each State on who should be Governor.

"These are just two thoughts which would give the Governors a little more to do, and probably put them in a position to contribute more to the College."

Dr. Maurice C. Pincoffs spoke at length in favor of State meetings, as opposed to multi-State Regional Meetings. He predicted that gradually in various States situations will arise which have already arisen in Maryland, in which the local membership of the College is either trying to abdicate its leadership in Internal Medicine, or is going to have to take on some new responsibilities. He referred to the action of many State medical societies in taking on responsibility of supervision of care of veterans in the office, in the home and in the hospital, by physicians in the State, and said there is inevitably coming up questions as to the qualification of consultants who are paid by the Veterans Administration and whose qualifications are to a certain extent vouched for by the State societies that have taken on, as it were, a contract with the Veterans Administration.

Dr. Pincoffs suggested that the development should be toward some local organization of the College—members being asked by the State society to serve as an advisory committee in helping them to fulfill their responsibility of vouching for certain men as qualified specialists in certain fields—in our case, that of Internal Medicine. He said that if that responsibility is not met and a system of procedure worked out, then we have in a sense abdicated one of our functions in setting up a standard for Internal Medicine. Dr. Pincoffs pointed out that the same thing bears on the relationship of local representatives of the College and the State to such things as consultant care and selection of consultants; more and more there is no question that the medical profession is organizing itself in connection with the movement for medical care of one kind or another; as long as we are in the forefront and the ones who guide it, we shall be meeting a public demand and the effort is sound. Dr. Pincoffs further stated that he thinks the College is going to be called on to play a part, and that part will be at the local level; the stronger the State organization of the College, the better it can take leadership in its field.

Dr. Edward L. Bortz spoke to the question, saying that there has been comment from time to time about the competition between large multi-State Regional Meetings and the regular Annual Sessions of the College, and expressed his entire accord with the comments of Dr. Dowden. Dr. Bortz bespoke an opportunity for younger men in the College to appear on the program of State meetings, thus giving them an opportunity to "win their spurs." He also said that the State meetings would offer a splendid opportunity for the membership of the College to meet likely young doctors who are aspiring to Associateship. Dr. Bortz felt that the program of the State meetings would be of a different character than the large multi-State meetings; that they do not require top flight features and big names, or speakers from long distances.

*Report* of the COMMITTEE ON EDUCATIONAL POLICY—Dr. William S. Middleton, Chairman: "The Committee on Educational Policy starts off with no brief, and has only the future in prospect. Of course on the background of the development of the educational policy of the College, there are certain definite ends that are apparent in the planning of the task. We have, first of all, the annual and regional meetings; the annual sessions have had a certain pattern that apparently arose from the individual initiative of the several successive Presidents. There has been no continuing policy and the Committee yesterday explored the possibility of setting up a program or a council on scientific work, perhaps extending the function of an already existing committee, so that that committee being one in continuity, a standing committee, if you will, could have a projected vision in the organization of the program.

"There was considerable resistance on the part of one member of the Committee, with myself, Dr. Morgan, Dr. Moffatt and Dr. Paullin who attended the Committee meeting. From the present viewpoint, in other words, it did not seem wise that the existing plan of making the President responsible for the program be altered. There was clearly, however, a division, and the two Committeemen there felt strongly that

there might be a change in the allotment of time, so that the annual program might find greater representation in the clinics, panels, the round tables, the clinical and pathological conferences.

"As one goes about the country, as one looks into the organization of successful meetings, he is struck by the fact that the general sessions are ever decreasingly attended and the attention to the clinics and the smaller demonstrations is apparently a growing tendency. I believe that this particular area of development will certainly be explored by the President-Elect, whether it has earlier attention, I do not know, but the Committee on Educational Policy felt that there was certainly a direction of exploration that put an increasing responsibility on the Chairman of Local Arrangements and on the strength of certain of the meetings of the past. For example, here in Philadelphia recently and in St. Louis some years past, the meetings depended upon the strength of the clinical organization. The regional meetings have varied in their representation and effectiveness in considerable measure dependent upon the time, attention and thought given to their development.

"As I have gone over some of the programs, I have investigated the reaction of our attendance upon such programs and I felt that there was perhaps more strength needed, and it may be that Dr. Bortz's suggestion that the younger men be used has lent itself to their broadening, but has not given as great strength to the older men who were attendant upon them, as we might desire.

"In other words, the Committee as a whole felt that the regional meetings could definitely be strengthened and should be studied with a little bit closer scrutiny by the Committee on Educational Policy. The greatest strength of the past, the greatest contribution to the educational effort, particularly affecting individuals widely spread over the country in the post-war period returning from military service and individuals who were in the period of development from the residency stage to the Associateship and Fellowship, has been in the Postgraduate Courses. I think that there has been no direction of educational effort that has been more widely acclaimed or more generally accepted as a real function of this College. Dr. Bortz deserves particular credit for the organization of these courses and the Committee will hold itself responsible for careful study of that in the future.

"In this direction, Dr. Fitz had written to me from his Committee, asking support of the Research Fellowships. That matter has already been covered and the appropriate grants to strengthen these fellowships have been made available from the College. The Committee on Educational Policy felt it was an unusual source of strength, a proper function of the College, to offer this particular outlet to oncoming men, the leaders of medicine in the future.

"The ANNALS OF INTERNAL MEDICINE has served a very important educational function in the zone of influence of the College and, as pointed out by its Editor, the influence has extended well beyond the membership of the College.

"There was one suggestion that may bear fruit. It has been at least proposed by this Committee that there be offered a sheet, or a page or two, in the ANNALS devoted to significant contributions. The Editor will not necessarily have to list those contributions each month or every two months, or bi-monthly, but he can certainly have the council of members or Fellows of the College in their special fields write as to what they feel in their field has been the outstanding contribution in the period of time given. This is not an effort to start an abstract section, but rather an indication of the trends in medical advances.

"There was one problem placed before the Committee that we did not deem was in our purview, namely, that of establishing a rating function. To be specific, the Memorial Hospital in New York asked that the American College of Physicians give their recognition to certain fellowships that were being established at the hospital. The Committee pointed out that there was only one current rating agency, namely,

the Council on Medical Education and Hospitals of the American Medical Association, and the Committee did not deem it wise for the College to enter into that area."

. . . On motion by Dr. LeRoy H. Sloan, seconded by Dr. William D. Stroud, and carried, the above report was accepted. . . .

Dr. Morgan requested an expression from the Secretary relative to the directorship of educational activities in the College. Mr. Loveland replied that he felt the educational program was progressing with facility through the coöperation of the Advisory Committee on Postgraduate Courses, the Committee on Fellowships and Awards, the President's Office and the Executive Offices. He referred to the great effort necessary to obtain adequate facilities, faculties and directors to conduct the Postgraduate Courses, pointing out the fact that the College program is conducted on a very much different plan than that for undergraduate and purely review instruction. Dr. Bortz, Chairman of the Advisory Committee on Postgraduate Courses, works in close coöperation and frequent contact with the Executive Offices; directors are selected from among those in whom we have absolute confidence in their ability, insight and wisdom in organizing the proper sort of courses with the proper content and conducted according to the best policies. It would be quite impossible, Mr. Loveland said, to require each of these directors to submit their full programs months in advance, so that they could be surveyed by the Committee on Educational Policy, but all outlines are reviewed by the Chairman of the Postgraduate Committee, and present conditions may eventually change, so that course contents may be obtained longer in advance, in order to have them reviewed by the Committee on Educational Policy. At the present time our directors carry such heavy burdens of teaching and administrative work, and faculties are carrying such a load that it seems unreasonable to demand that they submit their full and detailed outlines many weeks or months in advance of their publication. Mr. Loveland further stated that if the educational program and the Postgraduate Courses are expanded much beyond the present volume, the College may need a man to devote his whole time to work with the Committees on Educational Policy, Postgraduate Courses and on Fellowships and Awards, but under the present program, the College is getting along very well indeed.

*Report* of the ADVISORY COMMITTEE ON POSTGRADUATE COURSES—Dr. Edward L. Bortz, Chairman: "There has been a very definite, marked and spectacular increase in the number of individuals who desire to take the College courses. In 1946 there was an oversubscription in the majority of courses, and a very satisfactory response on the part of those who were asked to organize and direct the courses. There are certain limitations in giving these courses. The load and demands on teaching institutions and teachers who are appropriate individuals as directors of courses are such that we are surprised at the number of acceptances received. Over a period of time one gains experiences that help a great deal in formulating a policy in regard to selecting courses for the future, and contributory to those experiences are the responses from the men who take the courses. For example, one of the valid criticisms has been announcing that an occasional director may use young men who have limited experience and who resort to the literature for outlining their lectures, rather than talking with authority from experience. We have to have teachers of high quality, and the lecture and demonstration must be well prepared before delivery."

Dr. Bortz said the Committee must do the best it can for the present, with regard to one, two or three weeks courses, according to the teachers, material and directors at hand. The Committee had planned about fourteen courses for the spring and an equal number for the autumn of 1947, but probabilities are that this number will have to be somewhat diminished, due to exigencies that may develop. Through the Executive Secretary the Committee is in contact with teachers and faculties of various medical schools throughout the country, and the program is being outlined well in advance. He pointed out that in certain fields, notably Cardiology, there is always wide popular demand. The spring schedule includes courses in: Growth, Isotopes and

Tumor Formation; Cardiovascular Disease; Peripheral Vascular Diseases; Arthritis and Allied Conditions, Internal Medicine. The program will be announced from month to month in the ANNALS, and the Postgraduate Bulletin published about January 1. The Committee has received splendid support from the Governors and teachers who have given valuable suggestions. The Committee is eager to have any comment from the members of the Board of Regents at any time. Dr. Bortz further said that the matter of collateral reading has been considered some years ago. There was brought up for consideration by this Board the suggestion of publishing under different headings, Cardiovascular Disorders, Gastrointestinal Diseases, Hematology, etc., suggested reading of important new advances described in the literature. The Committee expects there will be some way of working these lists into the ANNALS OF INTERNAL MEDICINE from time to time.

*Report* of the HOUSE COMMITTEE—Dr. William D. Stroud, Chairman: "The House Committee, consisting of Dr. William D. Stroud, Chairman, Dr. T. Grier Miller and Dr. Charles L. Brown, with the Executive Secretary, Mr. E. R. Loveland, held a meeting at the College Headquarters on Tuesday, October 1, at 5:30 p.m. Following the Committee meeting, at the direction of the Committee, Mr. George W. Pepper, Jr., Architect, went over in person at the College Headquarters the various items under consideration, and his opinions are added after each item under consideration, as follows:

"(1) Installation of a door between the private office of Mr. Pindar, Assistant Executive Secretary, and his general office, on the second floor front.
This is an item obviously needed, presents no structural or expensive problems and is recommended.
In this Mr. Pepper concurs and estimates cost at $200.00."

. . . On motion made by Dr. William D. Stroud, seconded and regularly carried, this recommendation was approved. . . .

"(2) Installation of a kitchen on the third floor for the caretakers. This would entail covering the floor with linoleum in a room that is already appropriate and available, installing an electric range and a sink.
The caretakers heretofore have utilized the kitchen in the basement, which room is now urgently needed as a machine room for Addressograph, Graphotype, duplicating apparatus, etc.
Mr. Pepper finds no structural problem, considers the proposal practical, and roughly estimated the cost at around $800.00."

. . . On motion by Dr. William D. Stroud, seconded and regularly carried, this recommendation was approved. . . .

"(3) The conversion of the present kitchen in the basement to a machine room to house Addressograph machinery, duplicating apparatus and other equipment, thus to relieve the General Office on the first floor.
It is urgently and immediately needed that more space be made available in the General Office for the rapidly expanding files, stenographic staff, etc. The General Office cannot be efficiently administered under the present crowded conditions. Already several of the files have to be kept in the basement, where they are inconveniently located. Such a change would provide temporary relief only. Advantages, however, would arise in moving the noisy machines from the General Office, and providing some additional space for our workers and our files. These machines cannot properly be installed on the Second Floor, because of vibration and noise, nor would they be as convenient to the General Office as in the basement. Further, the operators of these machines are constantly referring to the

files. There is a dumbwaiter already installed between the General Office and the basement."

. . . On motion by Dr. William D. Stroud, seconded and regularly carried, this recommendation was approved. . . .

"(4) The possible installation of a caterer's kitchen in the interior of the basement, providing stove and sink, for use by caterer at Regional Meetings, Board of Regents' Meetings, etc.
Mr. Pepper finds this practical and obviously the only temporary solution to the relief of the General Offices. He points out that perhaps as a temporary measure we might not need to install a caterer's kitchen, but omit for the next year or two any functions requiring a caterer, or obtaining a caterer that can furnish his own warming cabinets."

. . . Dr. William D. Stroud recommended that this arrangement be left to the discretion of the House Committee, and this was approved by the Board. . . .

"(5) Enlargement of the College Building; an extension of the present rear wing to the west about forty feet, which would provide more than double the present space on the First Floor for the General Office and would provide also a large room on the Second Floor for files and clerical staff, or which could be used as a meeting room.
The larger quarters on the first floor have become a necessity. An effective and efficient General Office staff cannot be distributed around small rooms on the second floor, far removed from files and records. Furthermore, second floor rooms are needed for Committee meetings and conferences. The above expansion program would furnish adequate relief, it is estimated, for the next fifteen or twenty years. It would be in keeping with what might then be required for further expansion southward from this additional unit. The College must expect considerable expansion in the next twenty-five years. In the little more than ten years we have occupied the Building, the College activities have multiplied several times. We have an ever-expanding membership, with consequent expansion in files, equipment and staff. The business of taking care of the ANNALS OF INTERNAL MEDICINE alone is a major one, running into some $70,000.00 a year, the details being made up primarily of $6.00 and $7.00 transactions. Mr. Pepper carefully studied this situation and this proposal. He finds no obstacle structurally to match the rear wing of the building, to extend it and to keep it in conformity with the present architecture. He thinks it will in no way detract from the appearance of the building, that it will be practical, not only for the present, but for any necessary extension to the southward in future years to come. He believes that while the work can readily be planned now, construction should be deferred until present building conditions are improved, materials available and costs lower. This will probably be two years hence, but the preliminary work should be planned and completed during the interim, and such authorizations made as necessary.
Mr. Pepper's estimate for the building extension is approximately $40,000.00. Your Committee does not wish to recommend any appropriation of funds at this time for that extension, but would like authorization to ask Mr. Pepper to draw up plans for it."

. . . Motion of approval was made by Dr. Hugh J. Morgan, seconded by Dr. Maurice C. Pincoffs, and opened for discussion. . . .

Dr. Pincoffs suggested an amendment to the motion to provide that the House

Committee first obtain an estimate for the cost of drawing up the plans by Mr. Pepper. The amendment was accepted by Dr. Morgan, put to vote and carried.

*Report* of the CONSULTING COMMITTEE ON ANNUAL SESSIONS—Dr. David P. Barr, Chairman: "The President has taken seriously the matter of formation of the Annual Session program in Chicago. He has had the advice of many members of the Board of Regents as to subjects and the relative merits of subjects proposed. It is hoped to have a program which is representative of many interests of the College, and a close correlation among the afternoon programs, morning lectures, panel discussions and clinics. The program is still in the formative stage; help and advice are still solicited, particularly help which reflects opinions of Fellows of the College."

Dr. LeRoy H. Sloan, as General Chairman, reported that all clinics in Chicago have been contacted relative to the clinical program, and that the support of all medical schools and hospitals is assured. "Meetings with all the hospitals have been conducted in an effort to extend their vision and understanding of the contents, objectives and the type of attendants. We shall emphasize the basic sciences a little more than heretofore, so as to lift the level of the clinic and not simply to present cases of various kinds. The panel program is well underway. The General Chairman solicits the aid and advice of the Regents and of the Fellows at large in the clinic programs."

*Report* of the TREASURER—Dr. William D. Stroud: "The detailed financial statements of operation for the year 1946 will be presented in connection with the report of the Committee on Finance. You will then see for yourselves that the finances of the College are in very satisfactory condition. A year ago we had anticipated a deficit on the 1946 income, because of our expanded program of Clinical Fellowships, Research Fellowships and the resumption of the Annual Sessions. However, additional income, partially due to the majority of our members returning to civilian work from the Service and active membership in the College, continued growth in Life Membership Fees, increased income from initiation fees, a gift from the late Dr. James D. Bruce, and definitely increased income from the ANNALS, has resulted in our having an estimated surplus in our General Fund of about $17,000.00.

"Our investment counselors, Drexel & Co., periodically review the College holdings, and the Finance Committee receives monthly statements from the Executive Secretary's Office, thus enabling us to promptly and carefully administer the investment account. On our present invested capital our average yield is now 3.57%, and our investment counselors, in a report just received, estimate the annual income for the coming year at $13,585.25. The book value of our invested capital is $364,743.91, and the cash value on October 16, 1946, was $382,285.75, which shows an appreciation of $17,541.84."

. . . On motion by Dr. Maurice C. Pincoffs, seconded by Dr. T. Grier Miller, and carried, the report of the Treasurer was accepted. . . .

*Report* of the COMMITTEE ON FINANCE—Dr. Charles T. Stone, Acting Chairman, in the absence of Dr. Charles F. Tenney, Chairman: "The Committee on Finance met yesterday afternoon, October 19, 1946, in the absence of Chairman Charles F. Tenney and Roger I. Lee.

"The following report was compiled with the assistance of Mr. E. R. Loveland, the Executive Secretary, and to some extent with the assistance of President David P. Barr.

"The Committee wishes to report the receipt of a notice from the Probate Court for the County of Washtenaw, State of Michigan, advising that the American College of Physicians has been made a legatee in the will of the late Dr. James D. Bruce.

"The Committee receives and reviews the cash accounts of the College monthly; it is also from time to time canvassed with respect to certain investments and the sale of securities, as occasion arises.

"In accordance with the regulations of the Board of Regents, investments in the Endowment Fund must be approved by the Board as a whole. Since the spring meeting of the Board of Regents, the following security transactions affecting the Endowment Fund have been made:

*Called*

| | Endowment Fund | *Cost* | *Called For* | *Loss* |
|---|---|---|---|---|
| 6–27–46 | 50 Shares, Monsanto Chemical Co., Series 'A', $4.50, cum. pfd. | $5,878.60 | $5,500.00 | $378.60 |
| 6–27–46 | 4,000 Ohio Public Service, 1st Mort., 4s, due 1962 | 4,240.75 | 4,170.00 | 70.75 |
| | | | | $449.35 |

*Purchases*

| | Endowment Fund | |
|---|---|---|
| 8–21–46 | 50 Shares, American Smelting & Refining, 7%, Pfd. | $9,350.00 |
| 6– 7–46 | 5,000 Oregon-Washington Railroad & Nav., 1st, 3s, due 1960 | 5,300.00 |
| 8– 8–46 | 4,000 Texas & New Orleans Railroad Co., 1st & Refunding, 3¼s, Series 'B', due 1970 | 4,188.60 |
| 8–21–46 | 6,000 Texas & New Orleans Railroad Co., 1st & Refunding, 3¼s, Series 'B', due 1970 | 6,270.00 |

"For the information of the Board, the following purchases for the General Fund have been made since the last meeting, and are reported herewith for the information of the members:

*Purchases*

| | General Fund | |
|---|---|---|
| 6– 7–46 | 200 Shares, Commonwealth & Edison Corp., common | $7,218.24 |
| 6– 7–46 | 5,000 Oregon-Washington Railroad & Nav., 1st, 3s, due 1960 | 5,300.00 |
| 6–12–46 | 100 Shares, Philadelphia Electric Co., common | 2,962.50 |

"These purchases have in all instances been made upon the recommendation of the investment counselors. The Finance Committee receives periodically analyses of all College security holdings; the last was under the date of October 16, 1946, in which communication Drexel & Co., the investment counselors, recommended no changes in the present portfolio. It was recommended that $2,217.00 in cash available in the Endowment Fund be used to purchase 50 Shares of Pacific Gas and Electric Co., 6%, preferred stock, currently selling at about 40¼, to yield about 3.73%."

. . . On motion, seconded and regularly carried, this portion of the report was approved. . . .

"For some years past, the College has maintained a bank depository in the Dominion of Canada. The total amount of the deposit at present is $8,954.53. Drexel & Co. suggests, and we recommend, that $7,000.00 of this amount be transferred to our Philadelphia depository."

. . . On motion, seconded and carried, this portion of the report was approved. . . .

"When the last annual budget was prepared there was no knowledge that the College would receive the gift of $10,000.00 from the late Dr. James D. Bruce, which was announced at the spring meeting. This has been set up as the Bruce Fund, in accordance with directions of the Board of Regents. The fund has been invested in full in U. S. War Savings Bonds, 2½s, Series 'G', due March 1, 1957. The income of $250.00 per annum will be divided into halves, the first half for the founding of a

memorial award to the late Dr. Alfred Stengel and the other half allocated to an annual lectureship or award in the field of Preventive Medicine.

"When the budgets for 1946 were authorized it was anticipated that expenditures would exceed receipts by approximately $25,000.00. Actually the total income for 1946, based on actual figures for the first nine months and estimates for the last three months, indicate that there will be a surplus of approximately $54,000.00. This is not a true surplus, in that slightly over $25,000.00 received from Life Membership Fees and the Bruce gift go into the Endowment account and current outstanding obligations on fellowships of a little over $11,000.00 reduces the balance to approximately $17,000.00. In addition to the amounts received from Life Membership Fees and the Bruce gift, larger amounts than anticipated were derived from subscriptions to and advertising in the ANNALS OF INTERNAL MEDICINE.

"The Committee has studied the budget for 1946 and finds that the College has operated at less than budget appropriations in all departments except the College Headquarters, with a deficit of $59.56, and the ANNALS budget for the Executive Secretary's Office, with a deficit of $8,923.24, due to the big increase in the expansion of the ANNALS and in the cost of printing the journal. As a whole, the College operated at $19,628.57 below total budget appropriations.

"An estimate of income and expenditures for the year 1947 gives the following totals:

| | |
|---|---|
| Estimated Total Income | $158,700.00 |
| Estimated Total Expenditures | 153,296.61 |
| Balance | $5,403.39 |

"In the budget for the President's Office for the Twenty-eighth Annual Session, the Committee, after conference with President Barr, recommends that the amount allocated to traveling expenses, including guest speakers, be increased from $1,000.00 to $1,500.00.

"The Committee recommends that the salary of Mr. F. V. L. Pindar be increased from $5,500.00 to $6,000.00 per annum, effective July 1, 1947, in accordance with agreement at time of appointment.

"The Committee further recommends the adoption of the Budget for 1947 as a whole."

. . . On motion, seconded and carried, this portion of the report, including the adoption of budgets, with any additions specifically voted at this meeting, was approved. . . .

*"College Dues*—Fellowship dues were $20.00 and Associateship dues were $15.00, up to the end of 1932. At that time they were reduced from $20.00 to $15.00, and $15.00 to $12.00, respectively ($10.00 to full-time teachers, military officers, research workers, etc.). Everything costs materially more now; the College services and activities have been tremendously increased; the journal costs at least 35% more to publish, and the College cannot continue the desired expansions without increased dues.

"The present dues are considerably less than a number of other societies, such as the American College of Surgeons, the American College of Radiologists and others. We have been informed that the American College of Radiologists will increase their dues, if not already, to $50.00 per annum. We do not know whether the American College of Surgeons will increase its dues or not, but they have never been below $25.00 per annum. State medical societies have in approximately 50% of the cases increased their dues recently, the dues varying from $5.00 per annum up to $100.00 per annum. Furthermore, additional funds might well be used partially toward the proposed Building Fund for enlargement of the College Headquarters, which has been discussed by the House Committee. Many members feel our dues are exceptionally

low for the services we perform, and a return to dues of $20.00 and $15.00 for Fellows and Associates, respectively, and an increase to $12.00 for full-time teachers, military officers, etc., would meet, we believe, with the approval of the members at large. The Board of Regents has authority under the By-Laws."

. . . On motion by Dr. Maurice C. Pincoffs, seconded and carried, this portion of the report referring to dues was approved. . . .

"Interpretation of present regulations concerning fees of Medical Officers—When present regulations governing fees were adopted many years ago, members of the Medical Corps of the Army, Navy and Public Health Service were accorded fees under Class D—initiation fee, $10.00; annual dues, $10.00. At that time few, if any, Medical Officers received salaries adequate to enable them to pay the ordinary fees. The regulations, however, state 'included also in Classes B, C and D are members of the Medical Corps of the Army, Navy and Public Health Service.' A strict interpretation of this would mean that if a Medical Officer receives a salary of $5,000.00 or more per annum, he should pay an initiation fee of $50.00 and dues of $10.00; if his salary is less than $5,000.00, an initiation fee of $25.00 and dues of $10.00. To date, however, Class D has been reserved wholly for Medical Officers, and none of them has paid an initiation fee of more than $10.00. The question is whether this needs reinterpretation, or that we shall continue under the old precedent. This is submitted to the Board of Regents for discussion without recommendation."

. . . On motion by Dr. Maurice C. Pincoffs, seconded by Dr. Hugh J. Morgan, and carried, it was

RESOLVED, that the fees of Medical Officers remain as heretofore, due to the fact that the number of individuals affected is extremely small. . . .

. . . On motion by Dr. Charles T. Stone, of the Finance Committee, seconded by Dr. Hugh J. Morgan, and regularly carried, an honorarium of $100.00 was appropriated for the Secretary to the Treasurer, in consideration of her work for the College (1946 Budget). . . .

President Barr pointed out that the Budget as prepared and approved did not include certain items which were acted on at this meeting, as follows:

| | |
|---|---|
| $ 500.00 | additional, President's Budget |
| 8,000.00 | additional, Committee on Fellowships and Awards |
| 600.00 | increase in Salaries, Editor's Budget |
| 600.00 | (1946), House Committee |

These additional appropriations would wipe out the anticipated surplus on the budget prepared by the Executive Secretary, but on the other hand, the increase in dues will restore a small surplus.

Dr. James J. Waring brought up the matter of the traveling expenses for the Convocational Lecturer, the James D. Bruce Medalist and the John Phillips Medalist, and, after discussion, a resolution was regularly adopted providing that the traveling expenses of the Bruce Medalist be paid by the College. Precedent had already been set by which the College paid the traveling expenses of the Phillips Medalist and also of the Convocational Lecturer, where said lecturer is a non-member of the College.

President Barr brought up for discussion the matter of allowances made to Officers and Regents of the College for expenses when traveling on official College business, saying the regulations for the past many years has been that such expenses be limited to $5.00 per day in transit and $10.00 per day in residence, an amount which is now entirely inadequate to cover expenses. These same allowances are made to invited guests on the program of the Annual Sessions who are non-members of the College.

. . . On motion by Dr. Hugh J. Morgan, seconded by Dr. Maurice C. Pincoffs, and carried, it was

RESOLVED, that the traveling allowances be increased to $7.50 per day in transit and $15.00 per day in residence. This does not affect the regulations which also provide for payment of first-class round trip train and pullman fares, nor does it apply to Officers and Regents attending the Annual Sessions of the College.

*Report* of the AMERICAN BOARD OF INTERNAL MEDICINE—Dr. James J. Waring, Chairman: Dr. Waring had no formal report, but referred again to the preceptorship type of training for credit toward admission to Board examinations. Between this date and July 1, 1947, when preceptorships will terminate, Dr. Waring expressed the hope that some arrangements can be effected to reconcile all the differences of opinion and to make available resident or non-resident training that will satisfy everyone.

Dr. William D. Stroud inquired what method should be followed by a young man who is starting in hospital graduate training who wants not only to qualify for certification, but also for membership in the College. Dr. Stroud especially wanted to know how to obviate the situation whereby the young man might follow a plan approved by the American Board of Internal Medicine, which might not be approved by the Committee on Credentials.

President Barr replied that one of the purposes of the Survey Committee was to coördinate certain of these requirements between the American Board of Internal Medicine and the American College of Physicians, but said that this matter is entirely within the discretion of the American Board of Internal Medicine and the Credentials Committee of the College, and at present there are no rules that can be predicted.

Dr. Charles T. Stone commented that in his opinion it is unlikely that either the American Board or the College would take exception to residency training approved by the Council on Medical Education and Hospitals of the American Medical Association, which is the only accrediting agency for setting up and approving residencies for training. Furthermore, it was pointed out that both the American College of Physicians and the American Board of Internal Medicine have conference committees which work with the Council.

President Barr reminded the Board that the American College of Physicians appointed a representative to, and appropriated $1,000.00 for, the Council for Study, Prevention and Treatment of Rheumatic Fever, and asked for a report.

Dr. Stroud said that the Council has started a study of 10% of the 40,000 members of the Armed Forces that had rheumatic fever and are selecting a certain group with the help of the Veterans Administration in various parts of the country. Boards will be set up to examine these individuals, to determine if they had rheumatic fever and what their cardiac status is. There will be another 4,000 as a control group in the same towns, coming from the same boards. The study will cost about $500,000.00, which has been donated by an interested lady. Dr. Stroud further stated that the American Council on Rheumatic Fever now hopes the College will turn over its appropriated $1,000.00 for use in starting a national registry in the office of the American Heart Association. The money will be used for printing questionnaires and obtaining their return. In this manner it will be possible to learn just what the rheumatic fever and rheumatic heart problem is in this country.

President Barr announced that the next meeting of the Committee on Credentials will be held in Philadelphia, March 30, 1947, and the next meeting of the Board of Regents will be held at the Palmer House, Chicago, April 27, 1947.

Adjournment.

Attest: E. R. LOVELAND,
*Secretary*

## *OBITUARIES*

### DR. CLYDE MULHOLLON FISH

Thursday morning November 21, 1946, Dr. Clyde Mulhollon Fish, age seventy-one years, died of cerebral hemorrhage in the Atlantic City Hospital and was laid to rest in the town of his birth, Bath, Pa.

He was a student at Lehigh University and Rush Medical College in Chicago. He received his degree upon graduating from Jefferson Medical College in 1897. He served his internship in the Atlantic City Hospital and then followed a few years as an associate to Dr. B. C. Pennington at Atlantic City.

He then took up his residence in nearby Pleasantville, N. J. As his reputation as a diagnostician spread, his clientele came from all over South Jersey.

Dr. Fish was Superintendent of the Atlantic County Hospital for Tuberculosis until 1925 and Medical Director from 1941 until the time of his death. He became Director of the Tuberculosis League in 1919.

Dr. Fish became a Fellow of the American College of Physicians in 1930. He was a Mason, with membership in several Masonic organizations. He was a member and active in the following scientific organizations: American Federation of Sanitaria; National Tuberculosis Association; Aesculapius Club; The Medical Society of New Jersey; Past President of the Medical Society of Atlantic County; Atlantic City Academy of Medicine and the New Jersey State Tuberculosis League. He was active in the Kiwanis International.

Dr. Fish earned an excellent reputation as an internist and as an authority on tuberculosis. He was a very modest man; indeed, he was so modest and humble that he himself never realized his surprising ability and with modesty and humbleness he possessed the virture of kindliness.

DAVID WARD SCANLAN, M.D., F.A.C.P.

### DR. SYDNEY PEYSTER WAUD

Dr. Sydney Peyster Waud (associate), Chicago, Ill., died unexpectedly on October 19, 1946.

Dr. Waud was born August 23, 1909, in Oak Park, Illinois. He attended Princeton University from 1927 to 1931, following which he entered the Medical School at Northwestern University, from which he was graduated in 1934. Following an internship at the Presbyterian Hospital in Chicago, he did some post graduate work at Cook County Hospital. He practiced internal medicine in Chicago from 1936 to 1940. He was commissioned in M.C., A.U.S., in November of 1940, where he served with distinction until he was discharged in April, 1946, with the rank of Colonel. During his service, much of his time was spent overseas, the last two years

being spent in India. While serving in India, he developed a great interest in tropical medicine as well as in other infectious diseases which continued after his return to civilian practice. Following his discharge from service, Dr. Waud entered private practice in Chicago.

He was Clinical Assistant in Medicine at Northwestern University Medical School; Attending Physician, Veterans Administration Hospital, Hines, Illinois; and he was on the staff of the Passavant Hospital. He was a member of the Chicago Medical Society, Illinois State Medical Society, and the American Medical Association. He was also a member of the Chicago Heart Association, Association of Military Surgeons, and was an Associate of the American College of Physicians. He was the author of several published articles on various medical subjects.

Dr. Waud possessed a remarkable physical stature, and his sudden death at the age of 37 was a great surprise. He possessed great physical energy, and with this he coupled an unbounded enthusiasm and friendly good fellowship which he radiated both to patients and fellow workers. All who knew him believe that death has interrupted a promising professional career. His loss is sincerely felt by patients and associates alike.

LYLE A. BAKER, M.D., F.A.C.P.

## DR. HARRISON AYER CHASE

Dr. Harrison Ayer Chase, F.A.C.P., Falmouth, Massachusetts; born in Brockton, Massachusetts, December 11, 1877. Ph.B., 1901, Brown University; M.D., 1905, Harvard Medical School; intern, 1905–1907, Staten Island Hospital; postgraduate work, Harvard Medical School and New York Post-Graduate Medical School and Hospital; on the staff of the Goddard Hospital, Brockton, Massachusetts since 1909, having served in many capacities, including Physician-in-Chief; served at one time as Secretary, Vice-President, and President of the Brockton Medical Society. Member, Massachusetts Medical Society and American Medical Association; Fellow of the American College of Physicians since 1931; Diplomate, American Board of Internal Medicine; Director, Child Clinic, Brockton Visiting Nurses Association.

For many years Dr. Chase practiced both obstetrics and internal medicine. His chief interest over the years was obstetrics. He followed each new development with keen interest and its worth had to be proved to his satisfaction before it was adopted in his clinic.

Harrison Ayer Chase was a man of deep integrity, simple in his tastes, reserved yet deeply sympathetic and humane. He leaves a far reaching influence upon the community he loved and served for many years.

CHESTER S. KEEFER, M.D., F.A.C.P.,
Governor for Massachusetts